

The American Journal of **DIGESTIVE DISEASES**

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

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Volume 20

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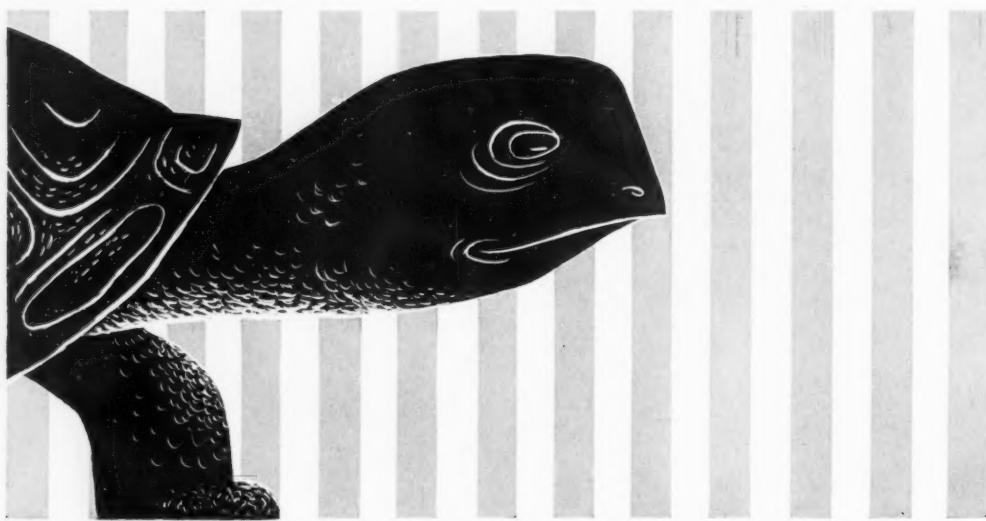
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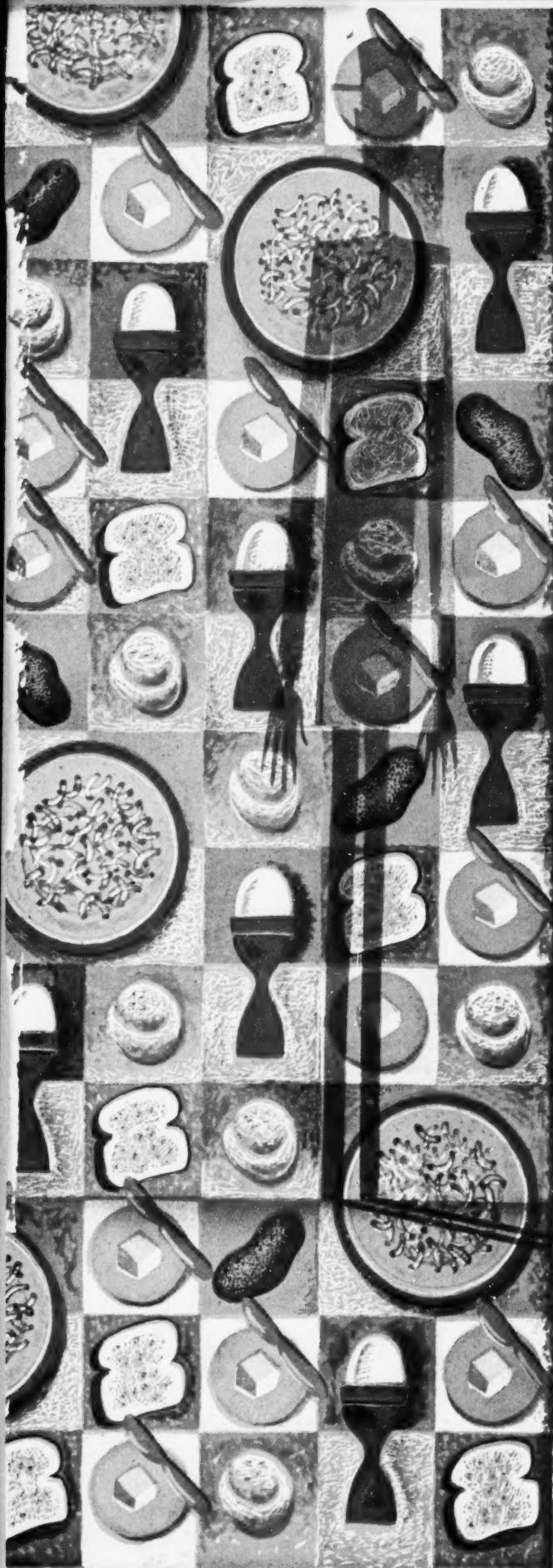
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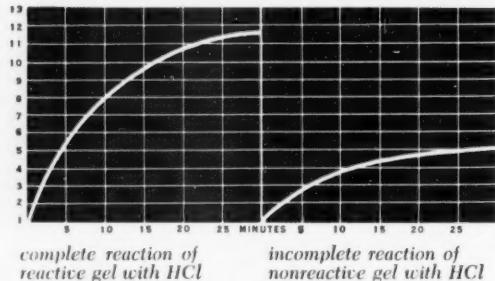
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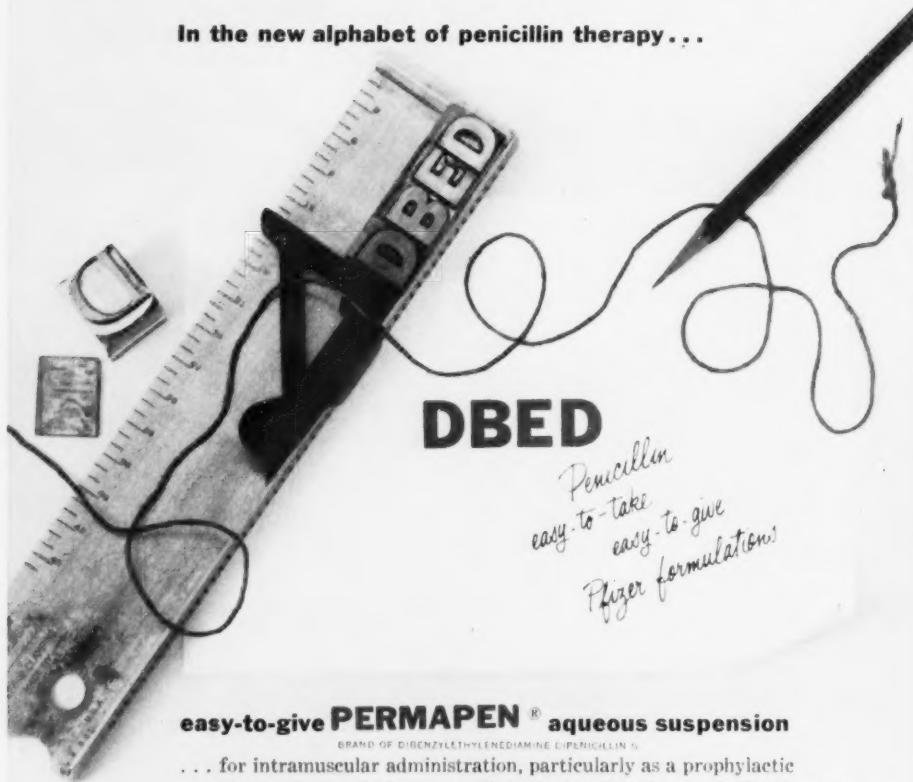
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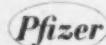
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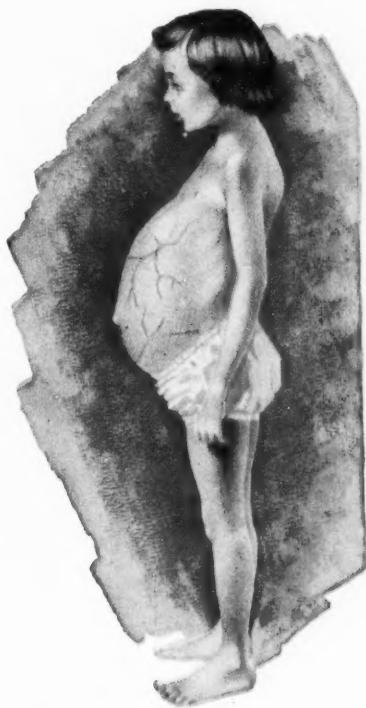
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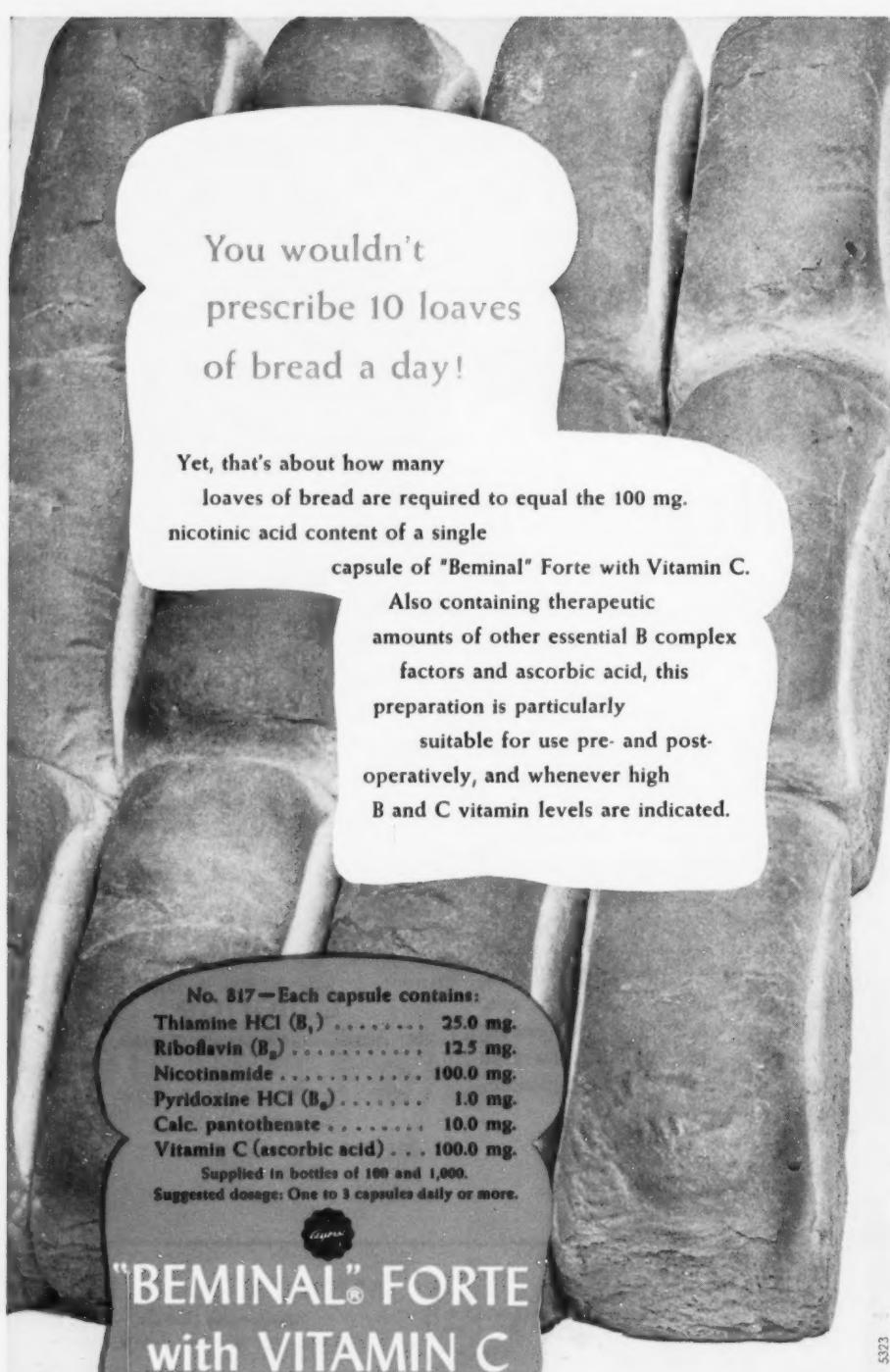
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FRONT AND SIDE-VIEW CHOLECYSTOGRAPHY, WITH A STUDY OF THE ANGLE OF VESICULAR ERECTION, OF THE VOLUME OF THE GALL-BLADDER AND OF THE VOLUMETRIC COEFFICIENT OF EVACUATION

G. ALBOT (1), J. TOULET (2), G. F. BONNET (2), AND C. MOULLART, Paris.

ALTHOUGH THE Boyden test has enabled cholecystography to reveal certain modifications in the tonus of vesicular contraction, up till now it has not been possible to form more than an approximate idea of the delicate anatomical lesions and various functional disorders of the gall-bladder.

These syndromes were not to be clearly defined until later with pre- or post-operative radiomanometry, then pre-operative radiomanometry by means of tapping the gall-bladder through the wall of the hepatic duct.

But these methods may only be used on patients who have been under study for a long time and concerning whom the operatory information is precise. There remain many purely medical cases in which it is necessary, while reserving them for an acceptable practical use, to perfect the current processes such as duodenal tubing and cholecystography, and in the light of numerous radiomanometric comparisons glean more and more accurate information from them.

As far as cholecystography is concerned, numerous and complex tests have enabled us to understand the shortcomings of current cholecystography and to perfect a slightly different technic which seems to us at present to give better practical results. (6 and 7)

DESCRIPTION OF METHOD

Our cholecystographic examination always comprises:

- (1) An exposure in standing position with compression.
- (2) A radioscopic centering in decubitus, during which the front-view projection of the bladder on the abdominal walls is marked with dermographic pencil.
- (3) A front exposure in decubitus with the bulb above and a distance of one meter between the bulb and the film.
- (4) A side-view exposure, in decubitus, without moving the patient, with the bulb on the left and the film on the right, the bulb being placed one meter away from the film. For this side-exposure a grille screen, or better still, a movable H "Potter-Bucky" screen is used which considerably improves the quality of the images.
- (5) The patient then takes the Boyden meal, and, to finish off, two exposures (one front-view and one side-view) are taken in the same man-

(1) Head of the Gastro-enterological Center of the Hôtel-Dieu, Paris. Home address: 202, Boulevard Saint-Germain, Paris 7e.

(2) Formerly "interne des hôpitaux de Paris". Assistant doctor at the Gastro-enterological Center of the Hôtel-Dieu.

Submitted April 30, 1953.

ner, an hour afterwards for a woman and 1½ hours afterwards for a man.

The distance we have fixed between bulb and film is arbitrary; but in any case the same distance should be kept during the examination as it is from these distances that the different coefficients used to determine the volume of the gall-bladder, according to our method, are calculated.

The ideal procedure would be to leave the patient undisturbed on the radiological table during the whole examination; the exigencies of current practice make this difficult. We therefore have our patients get up after the taking of the first three exposures; it is sufficient for the last two to have the patient in a position strictly similar to the first so that the calculations of volume and the appreciation of the various positions of the gall-bladder are not interfered with; this finding of the patient's position on the radiological table is simple since we are concerned with the position of strict decubitus.

This method requires only five exposures; the duration of the examination is not unduly protracted, and is generally adequate for the obtaining of the maximum amount of information.

To follow the exposures in decubitus, before and after Boyden's test, will form the object of special study. The projection surfaces should be measured on tracing paper marked off in millimeters and the "absolute vesicular volume" and the "volumetric coefficient of evacuation" will be calculated.

Finally, on the side-view exposures, we shall be able to appreciate the distance separating the base of the gall-bladder from the spine, and to ascertain the extent of the re-erecting of this base during the contraction well shown by the degree of angulation from the vesicular axis during this movement, in other words the "vesicular angle of erection."

2. CALCULATION OF THE VOLUME OF THE GALL-BLADDER

After 1926, Boyden was the pioneer of gall-bladder volumetry; but his method has the disadvantage of being too long for current practice. More recently G. Siffert has perfected a simpler method of volumetry calculated as in the previous method from antero-posterior and procubital exposures; it is still fairly complicated in its application. Furthermore, as these two authors have themselves pointed out, their results are not proof against certain errors which are avoided, thanks to the use of both front and side-view exposures, by the method of calculation perfected by one of our number (8) (receding effect due to the postero-anterior straightening of the gall-bladder axis, flattening from front to back or laterally, according to the case.)

Without entering into details and theoretical con-

siderations, let us merely state that our method is based on the assimilation of the gall-bladder to a perfect ellipsoid of revolution whose volume is easy to calculate if the surface of the principal sections, the longitudinal diameters of the sections, and the various correction factors to apply (the coefficient of photographic enlargement, the coefficient of reduction due to the receding effect) are known.

After the tracing on a paper marked off in millimeters, the surface of the vesicular projections is obtained, either by measuring with a planimeter, or simply by adding together the elementary surfaces

known from the squares on the paper. The vesiculovertebral angles in front and side-view are then measured. The length of the large axis of front and side exposures of the gall-bladder, which are often rectilinear, but sometimes also made up (in the case of an arc-shaped gall-bladder) of a succession of dotted lines, are also measured. It is then only necessary to multiply together the front surface and the side surface. The result obtained is divided by the measurement (in centimeters to one place of decimals) of the large axis of the front surface of projection. This last result is multiplied by a coefficient which is 0.51 for a front vesicul-

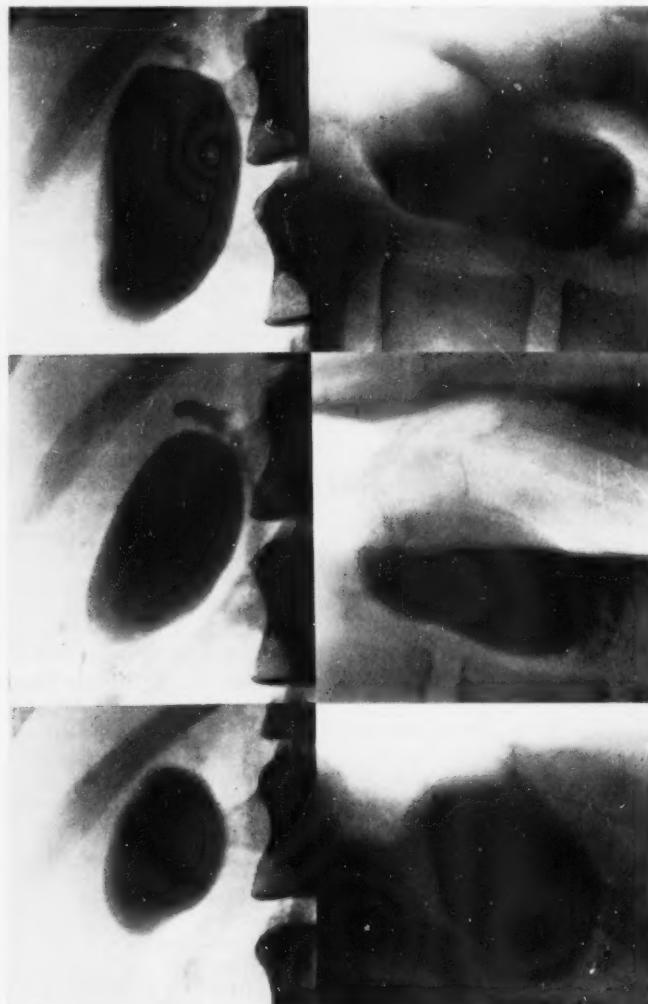


Fig. 1.—*Mme. Al. . .: Cysticitis, hypertonic stasis of the gall-bladder. Exaggerated vesicular contraction contrasting with inadequate volumetric evacuation, while front-views show an only apparent diminution of surface. (Telepaque, accelerated and minuted Boyden's test)*
 Above: cholecystography 12 hours after preparation; left in front-view, right in side-view.
 Centre: cholecystography 5 minutes after accelerated by iced serum Boyden's meal; left in front view; right in side-view.
 Below: cholecystography 30 minutes after accelerated Boyden's meal; left in front-view, right in side-view. The angle of erection is exaggerated (44°). The volumetric evacuation is inadequate (21%). In front, ball-shaped gall-bladder. The important diminution of surface under this incidence is only apparent and due to the re-erecting of the vesicular axis.

vertebral angle less than or equal to 40° , 0.63 for a front vesiculo-vertebral angle comprised between 40° and 45° and 0.75 for a front angle higher than 45° . The final result represents the absolute vesicular volume in cubic centimeters. (V_1)

These various operations may be carried out extremely rapidly with the aid of a calculating table or a calculating cylinder whose peculiarities we have described elsewhere.

The same determinations are made on the exposures taken after the Boyden meal. (V_2) and with the formula

$$\% = \frac{V_1 - V_2}{V_1}$$

the "coefficient of volumetric evacuation" is easily obtained.

Our research carried out on *normal subjects*, men and women, has enabled us to consider as physiological a vesicular erection angle between 5° and 15° in side-view, a volumetric coefficient of evacuation of 60% one hour after Boyden's meal in the case of a woman, and a volumetric coefficient of evacuation of 70% $1\frac{1}{2}$ hours after Boyden's meal in the case of a man. This last distinction is necessary, because in the space of an hour the evacuation reaches on an average only 50% for a man—a fact which confirms the results already obtained by Boyden.

It will be noticed that there exists a difference between the figures we are considering as normal and those, given by Boyden and by Siffert as normal also (80% evacuation). This discrepancy arises from the fact that the method of calculation used by these

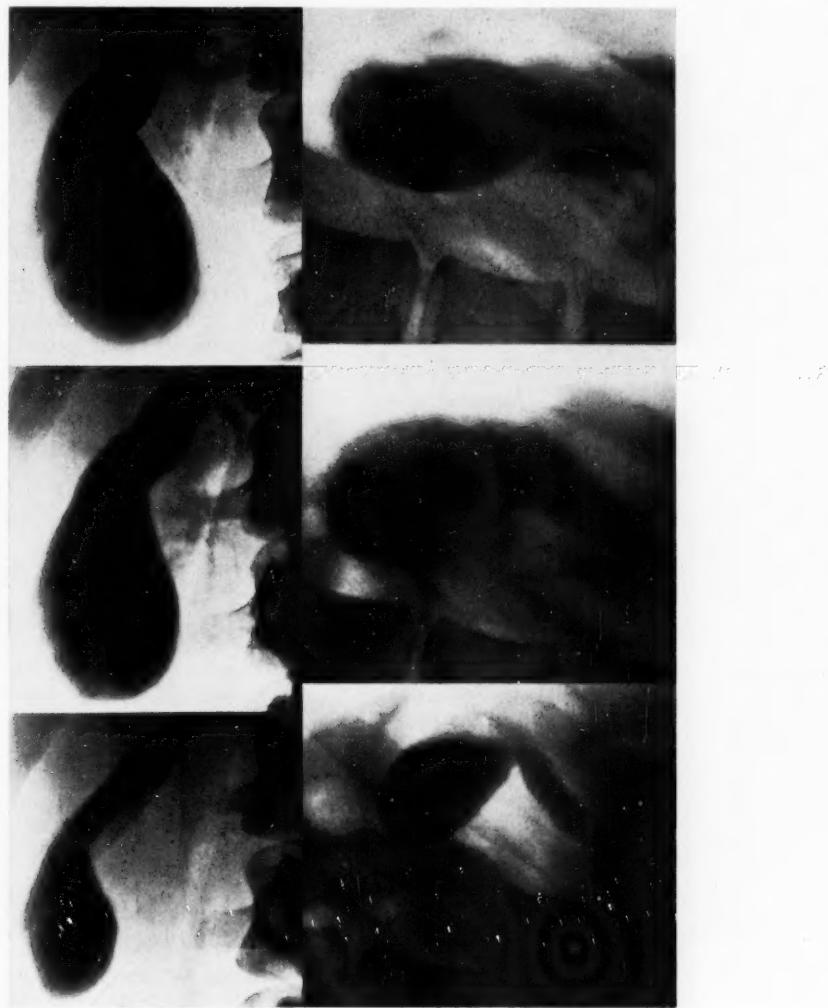


Fig. 2—*Mme. Del . . .: Localised infundibulitis (Telepaque, minuted and accelerated Boyden's test).*

Left: front-views. Right: side-views.

Above: cholecystography 12 hours after preparation;

Middle: cholecystography 15 minutes after Boyden's meal

Below: cholecystography 2 hours after Boyden's meal
One sees clearly on the side-views the roof-shaped contraction and the finger-shaped infundibulum. Important delay in the evacuation.

authors does not take into account the erection of the axis of the gall-bladder, visible only in side-view after the Boyden test; this erection adds to the real effect of evacuation an apparent diminution of the front surface by accentuating the obliquity of the gall-bladder. Our calculations, taking into consideration the value of side-view surfaces, eliminate the part played by the "receding effect," and therefore give a coefficient of volumetric evacuation lower but more accurate than that obtained by other methods.

3. ADVANTAGES OF FRONT AND SIDE-VIEW EXPOSURES, USING OUR DECUBITUS METHOD, OVER FRONT EXPOSURES IN PROCUBITUS USED IN CURRENT CHOLECYSTOGRAPHY

We have just seen that side-view radiography enables errors of judgment likely to be occasioned by the obliquity of the gall-bladder but to be corrected on the antero-posterior exposures.

Furthermore, the decubitus position has over the procubitus position the advantage of better molding by the opaque substance of the infundibulo-cystic region, the most frequent site of dyskinesia. The infundibulum is in effect, always situated in a more posterior plane than that of the body and the base of the gall-bladder and all the more so as the gall-bladder is more vertical (i.e. more perpendicular to the vertebral axis).

It is also in decubitus that the best view of the cystic duct and of the choledochus is obtained.

Finally, this position in which the patient is lying on his back, enables, without moving the patient, side-view exposures to be made whose indications are clearer in decubitus than in procubitus. These side-view exposures are not useful merely for the accurate and rapid calculation of the volume of the gall-bladder by our method; they also show up the spontaneous tonicity of the gall-bladder, (its hypertension or its hypotension) according to whether before any Boyden test it is horizontal, oblique or vertical: above all they enable the importance of vesicular contraction after Boyden's meal to be gauged by measurement of the "erection angle."

Our method may be combined with various pharmacodynamic tests, it may also be used to obtain a curve of chrono-volumetric evacuation: in that case only is it necessary to increase the number of exposures at more or less close intervals, taking care always to take front and side-view exposures each time.

It is in such a way that, with the greatest advantage, we combined our method with Busson's acceleration of the Boyden meal.

The radiological examination is then done in the following manner. A succession of exposures is taken in decubitus in front- and perfil-view. Then, the patient is turned round in procubitus for the ingestion of 100 cc of ied physiological serum and is left for five minutes in that position. Afterwards and still in procubitus he is given Boyden's meal to eat and has to stay in procubitus for five minutes more. This period of 10 minutes in procubitus is absolutely necessary to the regular acceleration of the fatty meal action.

The patient is then immediately put back in decubitus in front-view and a new succession of exposures, in front- and perfil-view still, is taken 10, 15 and 30 minutes after the Boyden meal. In this particular technie, this latter succession gives the same results as those obtained 1 hour after the

Boyden meal in the standard and accelerated technie. The subject may then get up and the last succession of front- and side-view exposures will be taken, still in decubitus in front-view, exactly 2 hours after the Boyden meal's absorption.

In this way, it is possible to obtain at the same time, an exact curve of the chrono-volumetric evacuation and, exact pictures of the cystic, of the choledochus and sometimes even of the intra-hepatic ducts or of the sphincter of the Oddi.

All these advantages explain the quality of the results obtained by this method.

a) *Details of the morphology of the biliary ducts.* Thanks to side-view exposures it is possible to judge the direction of the gall-bladder and to classify it into one of three categories defined in preoperative radio-manometry by M. Kapandji: a) horizontal gall-bladder whose axis is about parallel with that of the spinal column, b) vertical gall-bladder which is perpendicular to the vertebral axis, and c) oblique gall-bladder in an intermediate position. We have shown that this distinction has its usefulness in diagnosis: it would indeed seem that a spontaneously vertical gall-bladder, before any contraction test, is a gall-bladder which is hypertonic spontaneously or following on an obstacle in evacuation; a horizontal gall-bladder and one which remains so, is more likely a stasic or atonic gall-bladder.

On the other hand, some gall-bladders present bends at the level of their base, of their neck, or of the infundibulum. These bends are most often produced in a sagittal plane, giving rise on the front-view exposures to superpositions of opacity of difficult interpretation and which side-view exposures separate well: although it would be an exaggeration to attribute systematically a pathological role to the numerous anatomical variations in the biliary ducts, some lie at the origin of mechanical dyskineses and our method facilitates their detection.

Also from side-view exposures some irregularities of the cholo-cystic or cystico-choledoch junctions may be located.

b) *Better appraisal of the method of vesicular contraction.*

After Boyden's meal, the contraction of the gall-bladder may be studied in detail by means of side-view exposures, and therein lies their chief usefulness.

On the *front-view exposures*, vesicular contraction is revealed by two phenomena: 1° the vesicular shadow undergoes a complete elevation and an external deviation in relation to the ribs and the spinal column; 2° the front surface of vesicular projection contracts visibly; but this diminution in projection surface is more marked than it really is; it actually corresponds not only to the real diminution of the volume of the gall-bladder, but also to a difference in its orientation during the contraction.

It is on the side-view exposures that this modification of vesicular direction during the contraction can be appreciated: the vesiculo-vertebral angle has a tendency to become wider than it was, due to the erection of the body of the gall-bladder which in this way increases the distance between itself and the vertebral axis: it is therefore a matter of real "vesicular erection." We have already remarked that, in the case of healthy gall-bladders this straightening up is com-

prised within an angle of 5° to 15° from the initial angle.

Later we shall visualize the various irregularities in this vesicular straightening up: let us hasten to assert that knowledge of this phenomenon greatly assists the diagnosis of vesicular dyskinéses. The degree of straightening up of the gall-bladder effectively enables an appraisal of its effort of contraction to be made where the volumetric coefficient of evacuation takes into account only the actual emptying effect produced by this contraction. It is this distinction between the effort of contraction and the secondary effect of evacuation which is in our view an acquisition of paramount importance.

4. PRACTICAL RESULTS

1. Hypertension or cystic obstacles, chronic non-lithiasic cholecystitis localized in the infundibulum.

In all these cystic dyskinéses, front and side-view exposures enable us to describe a characteristic radiological syndrome.

a) *Clear cases of cysticites* are characterized in front and side-view cholecystography by a clear, normal or exaggerated effort of contraction and by feeble evacuation incompatible with the intensity of the contraction. Frontally after the Boyden meal, the gall-bladder undergoes an elevation, an external deviation and a rounding of its contours, which associated with atresia of the neck of the gall-bladder often involves a characteristic appearance of "ball gall-bladder." In side-view, the ball appearance simply corresponds to the erection of a tonic and contractile gall-bladder, but actually it empties very slightly or not at all.

It is such pictures which have enabled us to diagnose cysticites in the case of our patient Madame ALL . . . (fig. 1)

The patient was examined in dorsal decubitus by the front and side-view with Boyden's meal minuted and accelerated combined method (which yield at the 30th minute the same results as the classical method at the 60th).

On the front-view exposures taken after preparation, 5 to 30 minutes after the Boyden meal one can see clearly: the bladder getting in tension, the biliary ducts getting injected and, finally the surface of projection getting much lessened (50%)

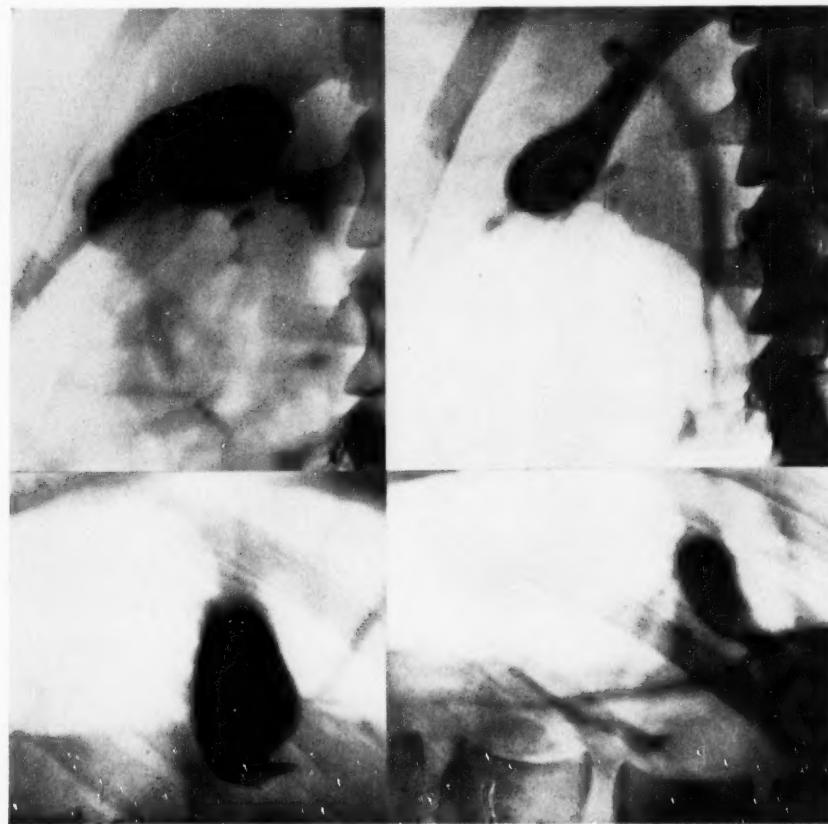


Fig. 3.—Mr. Per . . .: Hypertonic and hyperevacuated gall-bladder. Infundibulum's organic lesion revealed by the side-view cholecystography (Telepaque, classical Boyden's test)

Above: front-views; Below: side-views

Left: Cholecystography 12 hours after preparation;

Right: cholecystography 1h30 after classical Boyden's meal

On front-views one can appreciate accurately neither the intensity of the mitral tonus and of the contraction, nor the morphology of the infundibulum.

Side-views show the morphologic anomaly (beak-shaped deformation), revealing the spontaneous hypertonicity of the gall-bladder (which is perpendicular in relation to the spine), its contraction and its exaggerated evacuation (75%).

but tending to become "ball-shaped." With these front-views alone it would be difficult to give a precise diagnosis. Side-view radiographies taken at the same moments give particularly interesting information. While before Boyden's meal the gall-bladder is "horizontal," about parallel in relation to the spine, it may be seen getting more and more oblique till it gets nearly vertical at the 30th minute, this shows a particularly tense effort of contraction (angle of erection 44°) while the surface of projection does hardly diminish (18.7 cm² to 16.5 cm² that is 11% of the surface). Actually the diminution of the front-surface is only apparent and due to the change of orientation of the gall-bladder in relation to the direction of the rays.

The association of the two symptoms: clearly exaggerated effort of contraction (44°), clearly inadequate effect of evacuation (23cc to 18cc that is 21% of the volume), made us able to state the diagnosis of hypertonicity by cystic stasis gall-bladder.

b) *Infundibulites* present the same peculiarities: violent vesicular contraction with a raising of the base and a straightening of the axis (erection angle, 15°) contrasting with inadequate evacuation in view of the effort expended. But in this case the "ball" appearance is absent, and the evacuation, although inadequate, is more marked than in the preceding cases. Furthermore, an examination of the exposures after Boyden's

meal reveals quite a peculiar morphological image sometimes visible on the front-view exposures, but clearer on those in side-view, "*glove-finger shaped infundibulum*."

Sometimes even, this atresia of the infundibulum is of wide enough extent to produce a very clear angulation with the body of the gall-bladder, which Boyden's meal exaggerates still further, so much so that one has the impression of a vesicular shadow broken in two and raised in a "*roof shape*."

This condition was particularly visible in the case of our patient Madame DEL . . . (fig. 2) whose side-view exposure, after Boyden's meal well illustrates atresia of the infundibulum and the contraction in a "*roof shape*."

c) *Vesicular dyskinéses through mechanical anomalies*, (infundibulo-cystic bend, diaphragm, valvulated gall-bladder, segmentary adenofibromyomatosis) whether it is a matter of congenital malformations or lesions, or of acquired lesions, are at the root of vesicular syndromes, often difficult to diagnose.

Study of the side-views enables very clear morphological details to be obtained about these, whilst front-view radiographies remain silent on this point. Further,

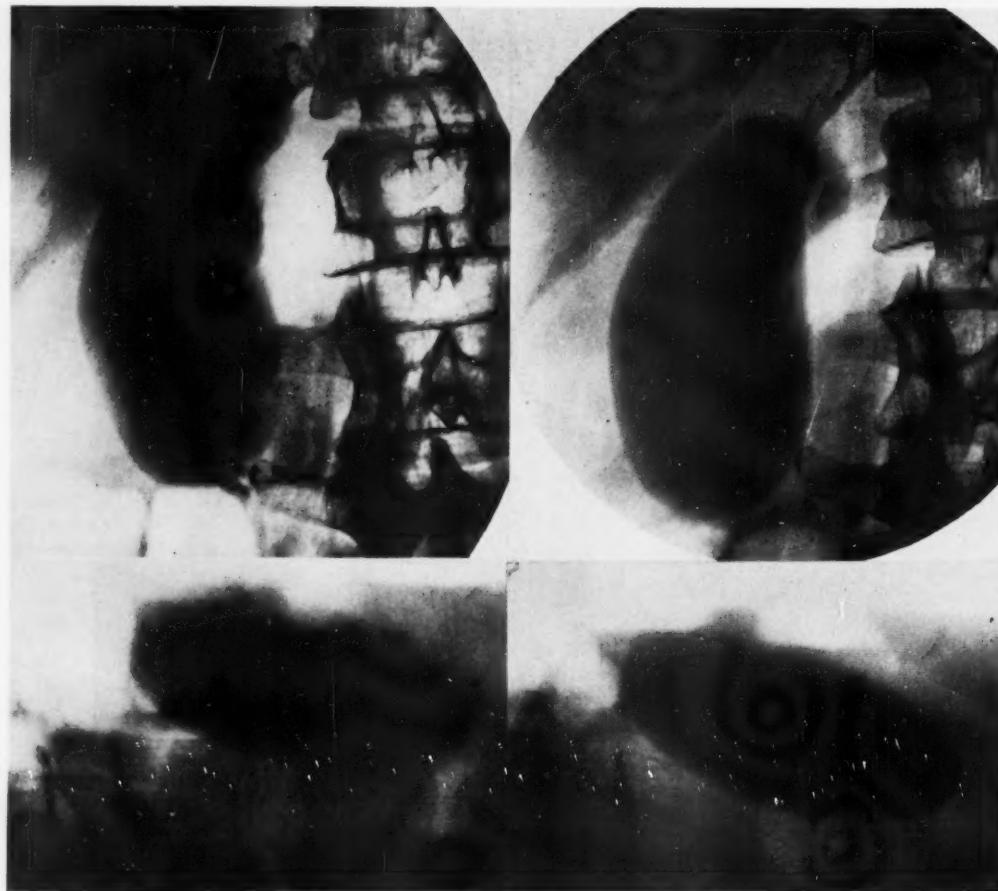


Fig. 4.—*Madame ZAMB . . . Asystole subsidiary to a cystic obstruction.* (Priodax: Classic Boyden's test) On the left, cholecystography after preparation; above, front-view in decubitus. On the right, 1 hour after Boyden's meal; above, front-view; below, side-view. Neither the position nor the projection surface of the vesicular shadow has varied; the volume remains 65 cm³; no sign of contraction; no evacuation. It is therefore a case of vesicular stasis.

the conjunction of front and side-view cholecystographies enables, as we have already remarked, the value of vesicular contraction to be distinguished from that of its evacuation. In this manner, unusual precision in diagnosis may be achieved.

Mr. Per's . . . front-view radiography (Fig. 3) did not reveal amorphologic anomaly which was clearly revealed in the side-view exposure as a brutal beak-shaped shrinkage. The vesicular hypertony could only be revealed on side-view exposure (vesiculo-vertebral angle in side-view: 62°). After Boyden's test, the vesicular erection remains the same and

the evacuation is exaggerated (75%) showing thus the vesicular irritability.

2. Biliary hypotension and Chiray and Pavel's cholecystatony.

They are opposed to the preceding syndrome. It is here most frequently a case of a gall-bladder whose volume has been slightly increased (60-70 cms³), horizontal, (parallel to the spinal column), of flabby appearance, easily following the shape of the neighboring viscera.

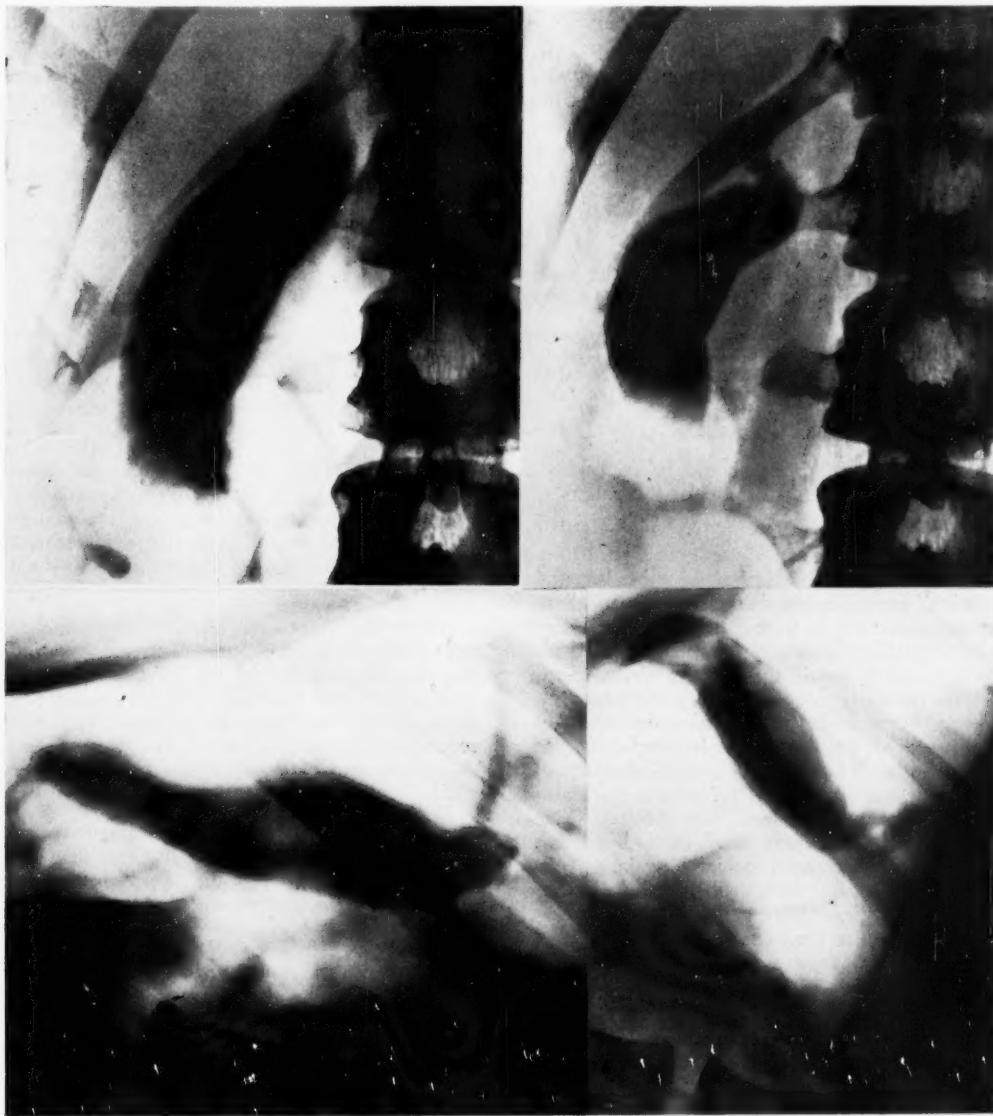


Fig. 5.—Madame PLAN . . .: A migraine sufferer with a hypercontractile gall-bladder. (Priodax: Classie Boyden's test).

On the left: cholecystography after preparation; above, frontal decubitus; below side-view decubitus; the gall-bladder is horizontal and voluminous.

On the right: 1 hour after Boyden's meal; above, front view; below, side-view. This last exposure reveals an exaggerated angle of erection of the vesicular axis (higher than 45°). The volumetric percentage of evacuation is high (71%). It is reminiscent of a hypercontractile gall-bladder without any cystic obstruction.

In the case of this confirmed migraine sufferer where no improvement was obtained by drainage of the gall-bladder, a simple antispasmodic treatment administered intra-venously caused spectacular relief of the disorders.

The ingestion of Boyden's meal only induces a slight tensing of the gall-bladder and the fact that this effort of contraction remains very slight is well indicated by a study of side-view exposures. The contraction can be shown externally by the signs in side-view previously described, *but attenuated*, that is by a slight change in the direction of the gall-bladder, the angle of erection being no wider than 5°. Sometimes it is an "arc of a circle" shaped deformation of the vesicular profile (the posterior outline of the organ becoming concave towards the column) or a "total recession of the vesicular body" from the column which alone betrays the slight tensing of the gall-bladder.

In this way therefore, an attenuated contraction with an attenuated evacuation, proportional to this effort of contraction, reveals the cholecystographic syndrome of cholecystostomies and is absolutely opposed to the syndrome of hypertension.

3. Total vesicular stases.

Under this head fall gall-bladders of large volume (greater than 60 or 70 cm^3) and which, on the side-views, remain horizontal without a sign of contraction and without evacuation after the usual delays.

This was the case of our patient Madame ZAMB . . . (fig. 4) where the examination of front and side-view exposures failed to reveal any marked modification before or after the fatty meal: no evacuation (0%), no indication of contraction (0°), initial volume of the gall-bladder was 65 cm^3 .

In this group, two categories should be contrasted, but they are very difficult to distinguish: the extensive early atonies, and total asystoles, subsidiary to an old cystic dyskinesia.

The data from anamnesis, clinical examination and from tubing is of great importance in these cases where cholecystography often fails to dispel hesitation. However the manifestation on the profile, after Boyden's test, of a slight contraction in the arc of a circle, seems to us to favor a slightly contractile gall-bladder; if this persistent function is accompanied by a slight evacuation, it could be attributed in preference to cholecystostomy. On the contrary, a total absence of evacuation would seem rather to point to asystole resulting from a cystic obstruction. The absolute value of the initial volume on the other hand, seems important to be found accurately for we consider very large gall-bladders, bigger than 70 cm^3 to be rather the accompaniment of subsidiary asystoles, whilst during atony, it was rare to see the volume of 60 or 70 cm^3 exceeded.

4. Hyper-contractile gall-bladders.

Front and side-view cholecystographies yield new information about the little known problem of vesicular hyperkineses. These hyperkineses have but badly defined limits from the normal; however they are able to explain certain disorders.

We have found accurately the normal figures of the volumetric coefficient of evacuation of the gall-bladder, which represents an average value which if not attained justifies the conclusion that there is a defect in evacuation: above these figures, one is faced with an exaggerated evacuation testifying to an abnormal hyper-functioning.

Sometimes, at the end of the Boyden test, the gall-bladder is already invisible; it also happens that it remains injected but with an exaggerated coefficient of volumetric evacuation, around or above 80%. It is then possible to detect on the side-views *signs of hypercontractility*, which are only the exaggeration of the normal signs of vesicular contraction, composed in the main of a brutal and exaggerated straightening up of the vesicular axis, the angle of erection greatly exceeding the 15° which we consider can be assigned as limit to the normal. (fig. 5 Mme. PLAN . . .)

This hypercontraction with hyper-evacuation may be the consequence of a vesicular irritation through a local lesion, for there, too, exists a syndrome of hypercontractile vesicular neurosis. Boyden had already pointed out, moreover, the case of gall-bladders which empty too quickly. Cholecystography in front and side-view, with volumetry, enables one to ascertain that they do so too brutally in a pathological manner, and to get at the same time figures of the degree of their hypercontraction and of their hyperevacuation.

SUMMARY

The systematic use during cholecystography of the incidences in side-view associated with the incidences in front-view, in decubitus, appears to us to mark an appreciable progress in the study of vesicular physiology and pathology.

By giving the maximum amount of detail of the morphology of the biliary tract, this method enables a balanced judgment to be made of the volume of the gall-bladder before and after Boyden's test, and thus permits exact figures of the volume of the vesicular content to be obtained.

Above all, it allows a separate study to be made of two phenomena very often confused, the *function of evacuation*, measured by the volumetric "coefficient of evacuation", and the *function of vesicular contraction*, measured by the "angle of erection" in side-view. A separate study of the two makes it possible to judge the variations which may be parallel or divergent.

With the help of these two very precise facts, it is then possible to perfect the radiological diagnosis of vesicular dyskineses and to distinguish normal gall-bladders, infundibulo-cystic hypertensions, cholecystostomy, total vesicular stases, hypercontractile gall-bladders.

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THE A- AND B-CELLS OF THE PANCREATIC ISLETS AS SOURCES OF THE ANTAGONISTIC HORMONES GLUCAGON AND INSULIN. THE SHIFT OF THE AB-RELATION IN DIABETES MELLITUS

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A NUMBER of recent experimental and clinical observations are not compatible with the classical conception that the islet-system of the pancreas secretes only one hormone, insulin. An alloxan-diabetic animal, for instance, requires more insulin than one in which the pancreas has been completely removed (26). Human diabetics in whom the pancreas has been removed completely require considerably less insulin after the operation (27). A part of this difference, of course, is due to decreased absorption as a result of the missing pancreas enzymes. The absorption of carbohydrates, however, is only slightly decreased, whereas the difference in the amount of insulin required before and after pancreatectomy is so considerable that it cannot be explained satisfactorily by an absorption deficit. Most of the commercial insulins, moreover, are accompanied by an effect called "initial insulin hyperglycemia" (3).

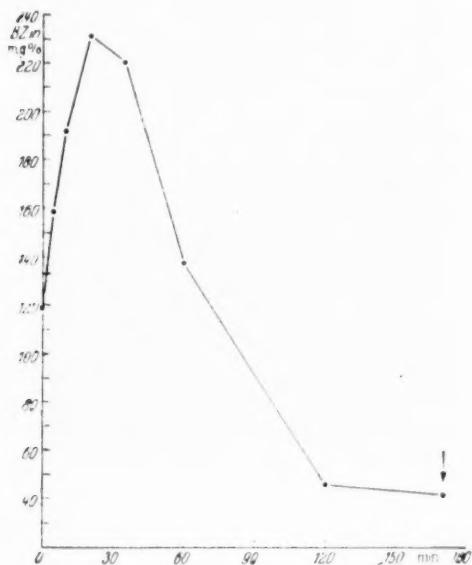


Fig. 1. Blood sugar curve following injection of a pancreas extract (1 mg N per kg body wt. i.v.) containing glucagon and insulin. Wt. of rabbit in fasting state 2340 g. The arrow denotes shock (From GAEDE) (14).

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OCTOBER, 1953

The phenomena mentioned may be explained by the fact that not only insulin, but also glucagon, a factor which elevates the blood sugar, is produced in the islets of LANGERHANS. *The cytological difference of islet epithelium manifested by the presence of A- and B-cells (also called α -and β -cells) is the expression of a functional antagonism.* Now it is clear that only the B-cells produce and secrete insulin; the A-cells, on the other hand, are the source of a substance capable of elevating the blood sugar by glycogenolysis in the liver. The A-cell hormone has been called the "hyperglycemic-glycogenolytic factor" or "Glucagon" (8, 13, 16, 24). With the two islet hormones mentioned the pancreas is capable of exerting a regulatory influence on the blood sugar level in both directions.

Cytologically the A- and B-cells are characterized by their specific granulations with differences in reaction to stains, histochemical behaviour and solubility (11). The nuclei of the two cell types show clear-cut differences only in the guinea pig; in man and other mammals they are not distinguishable. For reliable determinations of the AB-relation a clear-cut differentiation of the two cell types is essential. To achieve this, a certain amount of experience is necessary regardless of the method employed; this also pertains to improved modern procedures.

In the individual islet the relative number of each cell type found in the adult varies considerably. There is no question, however, that in most cases the number of B-cells definitely predominates. In some of the islets, however, most frequently located in the connective tissue of the larger ducts, there may be more A-cells. If, however, a greater number of islets (30 to 50) are counted out and averages calculated, the results for healthy adults (as well as for laboratory animals) show a constant relationship valid for all parts of the gland of 20% A- to 80% B-cells (6, 25). The method used was the silver impregnation of A-cells, a technique which, for quantitative studies in man, we consider superior to the staining of granula. With granula staining methods A-cell fluctuations were greater (10% to 40%) (17). The so-called D-cells comprise 3% to 5% of the islet cells in the adult; they are not found in the embryo and the child. There is some doubt as to whether D-cells may be regarded as a separate cell type; more probably they belong into the category of A-cells (17).

Slight variations of a few percent in the AB-relation

are to be considered as normal (silver impregnation counts), whereas greater fluctuations are indicative of a pathological situation. Age is an important factor; the figures named apply only to the adult. In the embryo A-cells are predominant. In the new-born the percentage of both is approximately equal; the number of A-cells decreases relatively with advancing childhood and approaches the adult formula at the end of the growth period (4, 11). The significance of this will be borne out in the discussion of the relationship of the anterior pituitary lobe to the islet system.

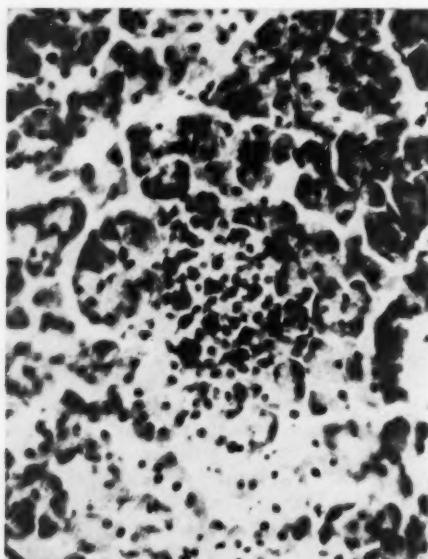


Fig. 2. Silver impregnation of islets of LANGERHANS in normal dog. A-cells dark, distributed over the entire islet, B-cells not impregnated.

B-CELLS AS THE SOURCE OF INSULIN

Today there is no question that insulin is produced, stored and secreted by the B-cells exclusively. The pancreas of animals with alloxan-diabetes in which the B-cells have been destroyed contains practically no insulin, although the A-cells are unchanged and comprise one-fifth of the islet volume.

The amount of insulin present in the pancreas depends upon the quantity of B-cells and the density of their granula (19). Under normal conditions the B-cells are capable to produce several times the amount of insulin required, as results of partial pancreatectomy have shown. The operative removal of four fifths of the pancreas and even more, corresponding to the loss of at least the same relative volume of islet tissue, does not lead to disturbances of carbohydrate metabolism under normal conditions.

There are no indications of a production of insulin in tissue other than the pancreas.

Cytological analysis of islet adenomas accompanied by pernicious insulism has corroborated the fact that the B-cells are the source of insulin. Such adenomas consist of giant B-cells with great variations in the density of granulation. In the endocrine nature the giant B-cells of adenomas are distinguished by the fact that they are not subject to the regulatory mech-

anisms directing the functioning of islet B-cells. They produce and pour out insulin irrespective of blood sugar levels manifesting a functional malignancy leading to extreme hypoglycemia. Their excessive insulin production is confirmed by the high insulin content and characteristic cytological criteria (1, 10, 25).

A-CELLS AS THE SOURCE OF GLUCAGON

The fact that B-cells may be brought about to disappear with alloxan has made isolated study of the A-cells and their functional significance possible.

Independently of each other *MURLIN* and *BLUM* were able to obtain pancreas extracts with a hyperglycemic effect, which led them to believe that, in addition to insulin, the pancreas must also contain a hyperglycemic principle (2, 23). It was not possible, however, to determine the tissue component responsible for this principle. *MURLIN* called it "Glucagon." As *BUERGER* was able to find this substance in circulating blood, and hyperglycemia could be produced by transfusion of blood containing glucagon, the assumption seemed justified that this substance is a physiological hormone of carbohydrate metabolism (3). That glucagon might possibly originate from the A-cells was considered as early as 1942 (7). It was not possible to corroborate this hypothesis experimentally before the studies of *THOROGOOD* and *ZIMMERMANN* in 1945. Chemical analysis of sclerotic and alloxanized pancreases in dogs and rabbits has rendered proof of the production of a "hyperglycemic-glycogenolytic factor" in the A-cells of the islet system (24).

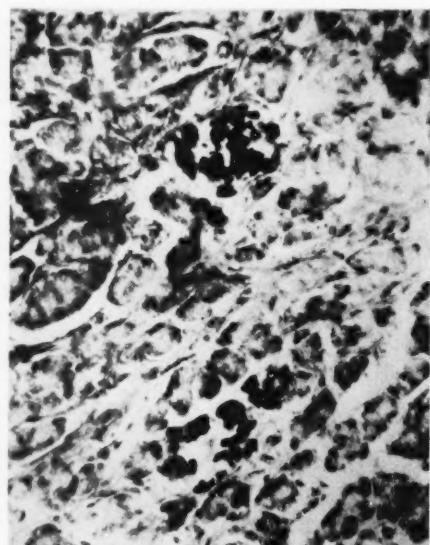


Fig. 3. Two islets of LANGERHANS in dog, consisting exclusively of A-cells, following ligation of ducts and 3 diabetogenic doses of alloxan. A-cells denoted by silver impregnation.

With the following procedure direct proof of the origin of glucagon from the A-cells of the islets could be obtained (16): The excretory ducts of dogs were ligated to produce atrophy of the excretory parenchyma. This produces no lesions in the islets, as a rule

there are no disturbances in carbohydrate metabolism. In approximately ten weeks degeneration of the excretory parts of the gland has taken place. In the second phase of the experiment the animals received weekly a diabetogenic dose of alloxan for three weeks in succession. On killing the animals the pancreas appeared as a shrunken cord-like structure of about the thickness of a pencil. Microscopic examination with specific staining methods showed that no B-cells and only a small rest of atrophic excretory parenchyma had remained. Smaller complexes of A-cells were found in the connective tissue of the pancreas or in what had remained of the atrophic lobules. By this procedure it was possible to obtain nearly isolated cultures of A-cells. Extracts of such tissue were free of insulin and contained relative high concentrations of the hyperglycemic principle. Since no other tissue components were present with the exception of connective tissue, the A-cells were the only possible source of the glucagon.

Reports of HALPOLE and INNES (29), that alloxan is ineffective following ligation of excretory ducts in sclerosed gland, could not be confirmed. The B-cells were also destroyed in sclerosed glands. The fact that this is followed only by a slight hyperglycemic effect may be explained by the macroglobular fatty degeneration of the liver ensuing as a result of the loss of excretory parenchyma of the pancreas.

In the rabbit an injection of glucagon not only increases the normal blood sugar level, but also produces a rapid rise of blood sugar during insulin hypoglycemia and shock with normal or even elevated blood sugar levels. The rapid but brief effect of glucagon contrasting with that of insulin is characteristic for the former.

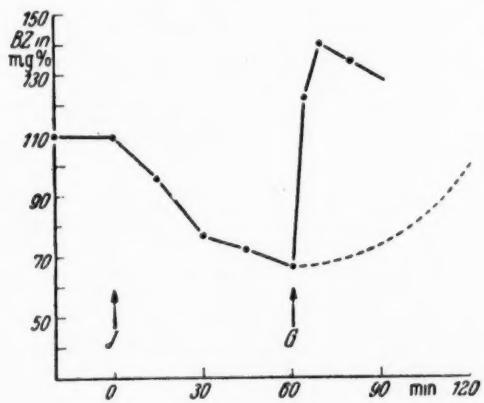


Abb. 4. Verabreichung von Glukagon

Fig. 4. Effect of glucagon injection (G) on blood sugar of a rabbit during insulin hypoglycemia. I: 0, 5 IU insulin/kg i.v.; G: Glucagon, 1 mg N/kg of a raw extract i.v. (From GAEDE) (14).

The occurrence of A-cells, unlike that of B-cells, is obviously not restricted to the pancreas. Glucagon has also been found in the mucosa of stomach and intestines of dogs and rabbits in regionally varying concentrations, however, in no other organs or tissues (24). Therefore it seemed logical to search for A-cells or

elements corresponding to them. In the basal areas of human stomach mucosa and in that of dogs granulated cells can be found in the epithelial gland structures which stain in the same manner as the islet A-cells (9, 22). Their distribution and frequency in the dog's stomach correspond in a conspicuous manner with the concentrations of glucagon found in the respective regions of the stomach by SUTHERLAND and De DUVE. Presumably intestinal A-cells will also have to be considered as a source of glucagon. The amount of glucagon produced by them is probably not less than that of the A-cells in the pancreas. The A-cells regularly found in the epithelium of excretory ducts of the pancreas which are cytologically and functionally identical with the islet A-cells may be regarded as transitional elements to the A-cells of the stomach and intestinal mucosa (15).

SHIFT OF THE AB-RELATION AND PREDOMINANCE OF A-CELLS IN EXPERIMENTAL AND HUMAN DIABETES MELLITUS

The normal quantitative relation of A- and B-cells as a source of glucagon and insulin is indicative of balanced carbohydrate metabolism indicated, among other things, by a physiological blood sugar level. The relation of the two antagonistic systems is obviously more important than the total volume of the islet organ. Neither a removal of larger portions of the pancreas, accompanied by a corresponding loss of islet tissue, nor the implantation of several pancreas organs is able to disturb the AB-relation, since there is no decisive shift in the relation between the two cell types. In total pancreatectomy both the A- and B-cell systems of the pancreas are eliminated, with the exception of

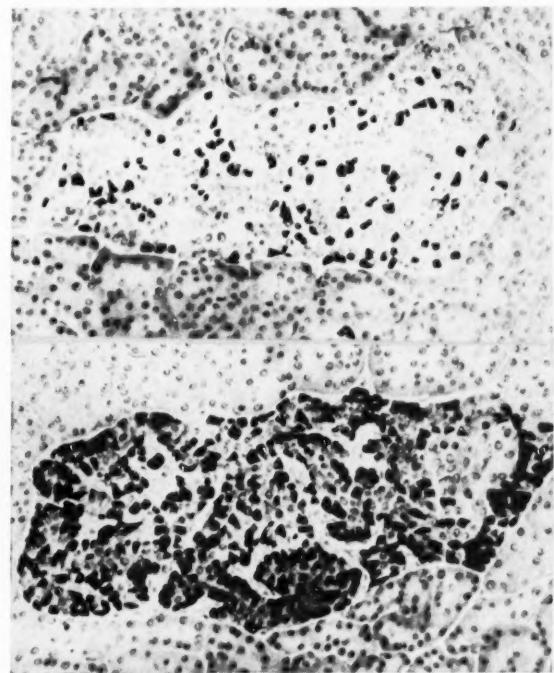


Fig. 5. Upper section: normal islet with normal cell relation. Lower section: islet in human diabetes with A-cells predominating. Black impregnation of A-cells.

the glucagon producing intestinal A-cells. It must be assumed, therefore, that they are responsible for hyperglycemia of diabetes following pancreatectomy. Since the A-cells are stimulated by an alpha-cytotropic principle of the anterior pituitary (12), a removal of this stimulus by hypophysectomy leads to an improvement of pancreoprivic diabetes (Houssay-dog) (9, 11).

An acute shift in the AB-relation and resulting effects in the alloxan-diabetic animal are very conspicuous. A destruction and disappearance of B-cells with the A-cell system remaining unchanged is equivalent to an extreme dislodgement of the AB-relation in the directions of the A-cells. The source of insulin is eliminated, that of glucagon unaffected. Whereas in the Minkowski-dog only the intestinal A-cells remain, the quantity in the alloxan-dog is greater to the extent of all of the pancreas A-cells. Does this not suggest an explanation for the higher insulin-requirement of the alloxan-dog as compared with the Minkowski-dog? If the alloxan-dog is pancreatectomized, pancreas-A-cells are eliminated and the insulin-requirement reduced by approximately one half.

As heterogeneous and different to noxes and measures employed to produce a permanent experimental diabetes may be, the last result in all cases is a reduction or elimination of B-cells and conservation of the A-cell system. *With respect to the islets of LANGERHANS a shift in the AB-relation and predominance of A-cells may be regarded as the specific substrate of experimental permanent diabetes.*

The destruction or elimination of B-cells may be accomplished in various ways: by operation in pancreoprivic diabetes, by exhaustion and degeneration in pituitary diabetes, by specific cytotoxic necrosis in alloxan diabetes. A permanent experimental diabetes without decisive reduction of B-cells is not known.

Cell differentiation of the islets in *human diabetes* bore out the same fact that the AB-relation is dislodged toward the A-cell-side (5, 6, 11). This finding demonstrates that islet alterations are the same in experimental and human diabetes, a fact not satisfactorily explained by WEICHSELBAUM's conception.

Of course the shift toward the A-cells in human diabetes, the cause of which is not exactly known, is only seldom as pronounced as in the experimental form of the disease. The relative percentage of A-cells in the islets is different from case to case and does not parallel the severity of the case and the insulin requirement. Cases of diabetes were found with barely significant increases in the relative percentage of A-cells (35% to 40%), on the other hand a case was seen in a four-year-old child in which the islets were composed of A-cells exclusively. The majority of cases is to be found somewhere between these two extremes. Especially pronounced (and absolute) predominance of A-cells was always found in childhood diabetes, i.e. in cases not manifesting islet changes in the sense of WEICHSELBAUM at all or only to a very unsatisfactory degree (11).

The diabetic AB-relation essentially pertains to all of the islets, i.e. the islet system as a whole. Even in partially hyalinized islets the A-cells are increased (25). So-called "atrophic" islets also consist for the

greater part or exclusively of A-cells, also the islets in islet-fibrosis. "Islet regenerates" and "rudimentary islets" often described in diabetes are not true islets; they consist of clusters of A-cells in which only a small number or no B-cells are found. They correspond to the islets normally found in duct tissue which—as we have already mentioned—are also complexes of A-cells.

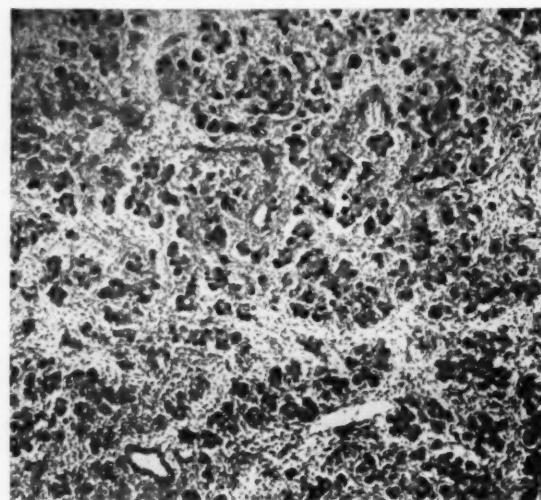


Fig. 6. Pancreas of human embryo (length 13 cm) rich in A-cells. Configuration of islets undeveloped.

Consequently, human diabetes is also distinguished by an increase of A-cells and a decrease of B-cells in the islets. In other words: the glucagon system predominates over the insulin system. The former seems to be the decisive factor, since in many cases of diabetes the remaining absolute quantity of B-cells based on experiences of partial pancreatectomy should suffice to cover the insulin requirement of the body. With respect to the islet organ it, therefore, seems more appropriate to speak of a dysfunction than of hypofunction in the case of diabetes.

The significant shift in the AB-relation toward the A-cells was confirmed for human diabetes by HESS (20) and by TERBRÜGGEN (25) who also made their cell differentiations by silver impregnation of A-cells. GOMORI (17), on the other hand, found an increase of A-cells only in the one half of the cases examined. Of seven diabetics examined he could find unequivocal increases of A-cells only in four cases. For the differentiation of islet cells he stained the granula with Chromhematoxylin-Phloxin.

A relative increase of A-cells is found not only in diabetics, however. In cases of prolonged undernutrition and in patients who have died of emaciating disease the AB-relation is dislodged toward the A-cell-side.

THE ALPHACYTOTROPHIC FACTOR OF THE ANTERIOR PITUITARY.

Heretofore, the islet organ appeared to be one of the endocrine glands not subject to a similar glandotrophic dependence upon the anterior lobe of the hypophysis as the thyroid, gonads and adrenals (28). Although

the existence of quite a number of anterior lobe factors with an action on the islet organ has been postulated, the decisive experiment to prove this, morphologic examination of the islets following hypophysectomy, has therefore not been able to demonstrate alterations in a conclusive manner. A number of authors have claimed that there is an increase of islets following hypophysectomy. If this were so, the hypophysis would have to exert a negative glandotropic effect in the islet organ. The majority of examiners have not found any changes in the islets following hypophysectomy, however (28). A conspicuous clinical finding of carbohydrate metabolism in hypophysectomized animals is their tendency toward hypoglycemia and insulin sensitivity. In a fasting state they may spontaneously develop hypoglycemic shock.

Since it could not be denied that by hypophysectomy only one of the two cell systems would exclusively or predominantly suffer an alteration a differentiation of islet A- and B-cells by staining methods was carried through in hypophysectomized rats and guinea pigs kept alive after operation for varying lengths of time (12). The survival time of animals following hypo-

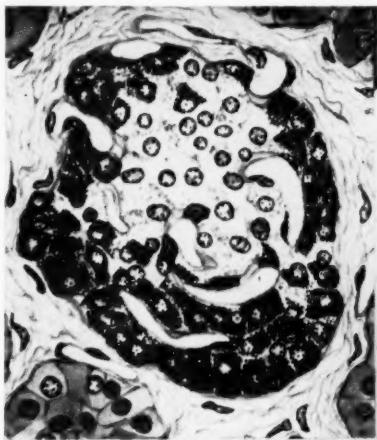


Fig. 7. Typical "Mantelinsel" from pancreas of the newborn. Black granulation of A-cells following silver impregnation. Location of A-cells and relative percentage differs from the adult.

physectomy varied from one week to nine months. In agreement with previous studies unspecific stains of the islets revealed no conspicuous alterations. With specific staining methods an *atrophy and decrease in the number of A-cells* could be found within a month following hypophysectomy, with no alterations of the B-cells. In many islet sections the A-cells had disappeared completely. On the average they comprised only 5% to 10% of the islet cells as compared with a normal percentage of 20% to 25% in rats and guinea pigs. Remaining A-cells often revealed signs of atrophy, they were small, as if compressed, with pyknosis of a part of their nuclei. These changes were found in all of the guinea pigs, but only in about one half of the hypophysectomized rats. Remarkably a normal cell picture was again found 5 to 6 months following the operation and thereafter. In single cases the impression was gained that the A-cells were hypertrophied, for instance in one guinea pig which was still alive 19½ months after hypophysectomy.

These observations indicate that by hypophysectomy a glandotropic effect, obviously restricted to the A-cells, is lost with resulting atrophy of A-cells. This alphacytotropic principle, on the other hand, is contained in extracts of the anterior pituitary lobe, daily injections of which produce an abnormal stimulation of A-cells and increased production of glucagon. Following such injections, a degranulation of A-cells has been observed (18). The B-cells endeavour to counteract the hyperglycemic tendency by an increased output of insulin. In the dog the resulting excessive demand on the B-cells, obviously especially vulnerable in the carnivore, led to their exhaustion and destruction. In rabbits, guinea pigs and rats, on the other hand, a compensatory increase of B-cells takes place which is sufficient to cover the increased functional demand on these cells. Hypophyseal diabetes does not ensue, the increase of B-cells leads to an increase in the total volume of the islet system and insulin content of the pancreas. The reaction of the human pancreas under these conditions is not known.

Since hypophyseal diabetes may be produced in the dog in the same manner by administration of highly purified growth hormone, the alphacytotropic action seems to be identical or closely associated with the former. The stimulation of A-cells and increased out-

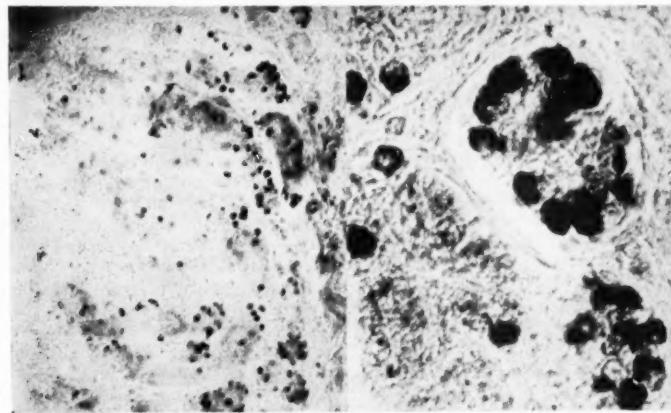


Fig. 8. Cells of gastric mucosa (fundus) of dog corresponding to islet A-cells. Silver impregnation.

put of glucagon by a principle of anterior pituitary lobe was also made probable by the results of investigations of *BORNSTEIN* and coworkers (1951). Their studies as well as those of *LAZARUS* and *VOLK* (1951) show that the hyperglycemic effect of growth hormone does not essentially take place via the adrenals.

An impressive contribution of the close association of growth hormone, alphacytotropic factor of the hypophysis and the A-cell-system were studies of the cell picture of the islets in human embryos and children (4). In this place of intensive growth the A-cells are considerably increased in comparison with the adult. The cell picture in the normal newborn is similar to that of the diabetic adult. In human embryos the A-cells of the islet organ predominate absolutely over the number of B-cells with approximately 50% of each comprising the islet cells in the newborn. With advancing childhood a relative decrease of A-cells takes place until, with the cessation of growth, a definite AB-relation has been established. In this connection the association of acromegaly and manifest or latent diabetes—which is not seldom—merits mention.

In the physiology and pathology of carbohydrate metabolism the realization that A-cells are the source of the hyperglycemic principle of the pancreas must receive due consideration in the future. Islet cell differentiation and a determination of the AB-relation seem to be of practical importance in this connection.

SUMMARY

The islet system of the pancreas is the source of two hormones. The B-cells produce insulin, the A-cells glucagon. By glycogenolysis in the liver glucagon is able to elevate the blood sugar level. In the healthy adult a normal AB-relation (20% A-cells, 80% B-cells) exists in the islet system which is indicative of balanced carbohydrate metabolism. In diabetes mellitus, in the permanent experimental as well as in the human form, the AB-relation is dislodged with A-cells predominating in number. The A-cells are stimulated by an alphacytotropic principle of the hypophysis, which is identical or closely associated with the growth hormone. Following hypophsectomy an atrophy and decrease in the number of A-cells takes place. In the embryo and during childhood, i.e. in intensive phases of growth, there is an absolute or relative preponderance of A-cells when compared with the AB-relation of the adult.

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THE ANOREXIGENIC EFFECT OF SUSTAINED-RELEASE DEXEDRINE PREPARATIONS

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d-AMPHETAMINE sulfate (Dexedrine) has had extensive clinical usage as a safe and effective anorexigenic agent (1-13). However, the effect of a single dose of Dexedrine is dissipated rather rapidly. Consequently, the drug must be taken at intervals during the day, usually three times daily before the usual mealtime. Frequently, between-meal hunger, especially in the late afternoon and before retiring ensues. Aside from discomfort to the patient, these episodes of hunger may cause deviations from the prescribed diet. Since a low calorie diet is the basis of a sound weight-reducing regime, any deviation from it will be reflected in the therapeutic results.

SUSTAINED-RELEASE DEXEDRINE

In order to circumvent, insofar as possible, any deviation from the prescribed dietary program, capsules of Dexedrine were prepared with a coating on each granule of Dexedrine so as to allow release and absorption of the drug at specified times after ingestion. Thus, it was hoped that a sustained therapeutic level could be maintained throughout the day.

The Dexedrine in the sustained-release capsule is present in the form of very small pellets. The pellets are so designed and coated so that a mixture of them will release the medication for a sustained period of time. The aim of this type of release of medication, as opposed to the results obtained by the conventional dose three times daily, is schematically illustrated in Figure 1.

From this figure, it is evident that when the medication in the sustained-release capsule is released at intervals A, B, C, D, etc., the therapeutic level of the

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Submitted Mar. 16, 1953.

medication may approximate a straight line, Z. Because of the overlapping of dosage in the shaded areas, the drug effect in the segments immediately above them is brought up to a therapeutic level. Moreover, because of variations in gastro-intestinal secretions and motility, a further scattering of the time of release of the drug occurs rather than a complete release at any sharply defined or calculated time. Thus, a continuous, smooth drug effect is obtained, rather than intermittent peaks of action.

The present study was undertaken with a view to answering the following questions:

1. Is such a sustained-release capsule of Dexedrine therapeutically effective as an anorexigenic agent?

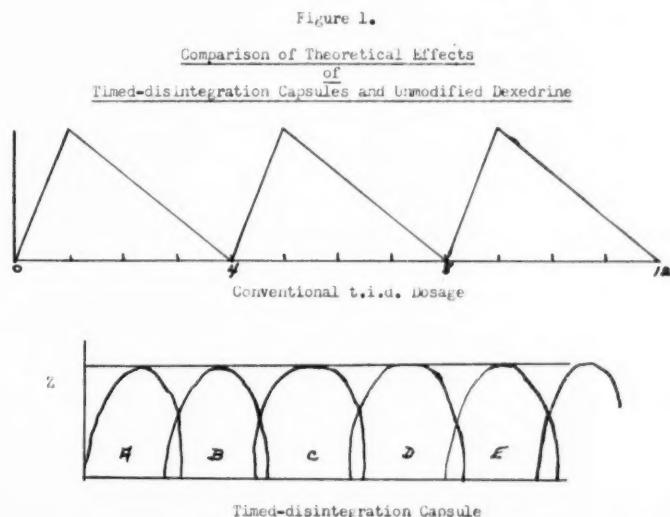
2. Is the use of such capsules attended by any change in the incidence of undesirable side effects?

At the time these observations were made, the final, commercially marketed, capsule had not been evolved. Therefore, this study was divided into three parts; each part tested a different capsule formula. Although each of these formulae differed in pellet release-time or in dosage, they all made use of the sustained-release principle, and it was not felt necessary to prove again in either the second or third experiment, conclusions which had been previously established.

FORMULA A

Materials and Methods

All subjects observed during this investigation were patients at the Obesity Clinic of a municipal hospital outpatient service. Most of the subjects were referred to us by other departments of the dispensary. Diabetic patients and patients with edema were not accepted for



this study. It was originally planned that each subject would be observed for a period of about 6 weeks on each of three medications—Formula A (which contained 15 mg. of Dexedrine coated to permit a smooth, even release of the drug), unmodified Dexedrine, and a placebo, each thus serving as his or her own control. Many patients, however, were lost from the study before such a program could be completed.

A total of 92 subjects were adequately followed. Of these, 38 were observed while on a course of each of the three medications (Group I). Thirty were observed while taking each of 2 medications; 13 while taking Formula A and unmodified Dexedrine (Group II), 10 while taking Formula A and a placebo (Group III), and 7 while taking unmodified Dexedrine and a placebo (Group IV). Of 24 patients who were observed while taking only 1 medication, 12 used Formula A (Group V), 3 used unmodified Dexedrine (Group VI), and 9 used a placebo (Group VII).

All except 3 of the 92 subjects were women. Their average age was 41 years, average height 64 inches and average initial weight 208 lbs. The deviation of weight from standard was plus 48% according to actuarial tables of standard heights and weights.

Formula A* was supplied in red capsules. Unmodified Dexedrine was supplied in 5 mg. capsules, some capsules being red and some white. Placebos were also supplied in red and white capsules. The reason for the different colors was to prevent the patient from knowing when any change in medication was made. In this way, subjective psychic influences were minimized.

The patient was always instructed to take a red capsule 20 to 30 minutes before breakfast, and a white capsule 20 to 30 minutes before lunch and dinner. Thus,

*All medications were made available through the courtesy of Smith, Kline and French Laboratories, Philadelphia, Pa.

while using Formula A, the patient would take the medication (red capsule) before breakfast, and a placebo (white capsule) before lunch and dinner. While using unmodified Dexedrine or a placebo, the patient would similarly take a red capsule before breakfast and a white capsule before lunch and dinner. In all cases, while using either form of Dexedrine (Formula A or unmodified), the total daily dosage was 15 mg.

At the time of the first visit of each patient, a history was taken and a physical examination was done. The cause of obesity and its treatment were discussed briefly, and the importance of rigid adherence to the prescribed diet was emphasized. Each patient was then referred to the dietitian for a diet.* The diet was similar for all patients and remained constant during the entire period of observation. It allowed 1060 calories a day, of which there were derived from protein 75 Gm., from carbohydrate 100 Gm., and from fat 40 Gm. It contained adequate amounts of minerals and vitamins. No supplementary vitamins were prescribed, nor was any clinical evidence of vitamin deficiency encountered in any of the patients. This diet was explained individually to each patient by the dietitian.

Each subject was also given one of the three types of medication and instructions as to its use as described above. Patients were rotated as to which medication was prescribed initially. Sufficient medication for 2 weeks was given, and each patient was instructed to return after that time. The pulse rate and blood pressure were checked at frequent intervals. Urinalyses, blood counts, and determinations of the basal metabolic

*We would like to express our gratitude to Miss Marjorie B. Whiting, dietitian to the Welfare Island Dispensary, whose patience and tact with these patients aided us immeasurably in conducting these experiments.

TABLE I
COMPARISON OF WEIGHT LOSS ATTAINED WITH FORMULA A,
UNMODIFIED DEXEDRINE AND A PLACEBO

Group*	No. of Subjects	Formula A		Unmodified Dexedrine		Placebo	
		Average Time Observed (weeks)	Average Weight Change (lbs. per week)	Average Time Observed (weeks)	Average Weight Change (lbs. per week)	Average Time Observed (weeks)	Average Weight Change (lbs. per week)
I	38	7.7	-1.1	8.0	-1.2	6.3	-0.5
II	13	7.1	-1.3	6.2	-1.2		
III	10	5.7	-1.3			5.6	-0.8
IV	7			7.0	-1.7	5.4	-0.7
V	12	5.6	-1.3				
VI	3			7.0	-2.2		
VII	9					6.0	-0.9
Average of all trials							
	73	6.8	-1.17				
	61			7.1	-1.15		
	64					6.0	-0.62

* Group I Patients observed while using each of the three medications.

Group II Patients observed while using Formula A and Unmodified Dexedrine.

Group III Patients observed while using Formula A and a placebo.

Group IV Patients observed while using Unmodified Dexedrine and a placebo.

Group V Patients observed only while using Formula A.

Group VI Patients observed only while using Unmodified Dexedrine.

Group VII Patients observed only while using a placebo.

rate were done on a representative group while on each of the regimes.

RESULTS

I. Effects Upon Weight Loss (Table I)

In all subjects who were observed while taking more than one medication, the averaged results for each were fairly constant. The average weekly weight loss was comparable while taking either Formula A or unmodified Dexedrine, and was about twice that observed when a placebo was employed.

Thirty-eight patients received all three medications in random rotation. The number 1, 2, or 3 was assigned to each medication to correspond to the order in which it was used in individual patients. By adding these numbers for each medication and dividing by the number of patients (38), the average order of use of each of these medications was determined. The average for each medication was as follows: Formula A, 2.0, unmodified Dexedrine, 2.2, and placebo, 1.8. Thus the ideal average of 2 for each medication was closely approximated.

Five of the 13 subjects observed while using Formula A and unmodified Dexedrine used Formula A initially; 5 of 10 subjects observed while taking Formula A and a placebo used Formula A initially; and 3 of 7 subjects observed while taking unmodified Dexedrine and a placebo were started with unmodified Dexedrine.

In addition to the 68 subjects who were observed while taking more than 1 medication, 24 subjects were studied who received only 1 medication. Twelve received Formula A, 3 received unmodified Dexedrine,

and 9 received a placebo. A total of 73 patients was observed while taking Formula A, 61 while taking unmodified Dexedrine, and 64 while taking a placebo. The over-all average weekly weight loss for the entire group again showed comparable results for both Dexedrine preparations. The average weekly weight loss when a placebo was used was about half that observed for the Dexedrines.

This comparison of weight loss obtained with Formula A, unmodified Dexedrine and a placebo was subjected to statistical analysis. It was necessary first to establish that the results obtained with one group on Formula A (or unmodified Dexedrine or placebo) were not statistically different from the results obtained with any of the other groups on the same medication. This, fortunately, was easily established, making it possible to compare the results of all patients on Formula A, with all patients on unmodified Dexedrine and with all patients on a placebo. It was concluded that there was no difference between the results obtained with Formula A and those obtained with unmodified Dexedrine, but that there was a high degree of significance between the placebo and the two Dexedrine preparations. The mean was 0.6 and $T = \infty$ in the case of the placebo. Both Formula A and unmodified Dexedrine were below the 10% levels of significance on the chart, and below the 10% level of significance of variation on the charts.

II. EFFECTS UPON CERTAIN CLINICAL AND LABORATORY EXAMINATIONS (TABLE II).

Comparison of frequently determined blood pressure and pulse rate examinations on all subjects observed,

TABLE II
SUMMARY OF CERTAIN LABORATORY AND CLINICAL DATA OBTAINED
USING FORMULA A, UNMODIFIED DEXEDRINE AND A PLACEBO

Item	Group*	Number of Subjects	Formula A		Unmodified Dexedrine		Placebo	
			Range	Average	Range	Average	Range	Average
Blood pressure	I	38	100/60 - 194/116	139/88	90/60 - 210/116	135/86	88/60 - 200/120	137/87
	II	13	109/58 - 232/116	143/85	118/74 - 216/118	139/86		
	III	10	108/67 - 166/94	135/82			106/64 - 190/100	137/83
	IV	7			102/68 - 195/122	136/87	100/68 - 186/112	137/86
Pulse rate	I	38	65 - 95	83	64 - 94	82	63 - 109	82
	II	13	67 - 94	80	68 - 100	81		
	III	10	70 - 110	86			65 - 100	85
	IV	7			65 - 96	81	70 - 104	83
Hb. (gms.)	I	19	11 - 16.5	13.5	10.3 - 16.2	13.9	11 - 15	13.6
	II	13	8.5 - 17	13.6	9 - 17.5	13.8		
	III	7	11 - 15.5	13.3			12.5 - 15	13.9
	IV	7			11.5 - 15	13.1	12 - 16.5	14.0
W.B.C.	I	19	5400 - 10,300	7680	6100 - 9800	7620	6100 - 11,500	7670
	II	13	5950 - 11,000	8210	6350 - 10,150	8320		
	III	7	5000 - 9950	7540			6500 - 9700	8190
	IV	7			7250 - 12,600	8970	6900 - 12,150	9300
Polys %	I	19	36 - 75	55	30 - 68	53	40 - 62	52
	II	13	40 - 70	55	44 - 66	54		
	III	7	48 - 70	56			32 - 70	55
	IV	7			54 - 70	59	60 - 70	64
Basal metabolic rate	I	20	-10 - +28	+6.2	-16.5 - +37	+8.5	-13.5 - +23	+8.4
	II	13	-12.5 - +19.5	+1.1	-11.5 - +20	+2.8		
	III	6	-1 - +16	+8.5			-6 - +24	+6.2
	IV				-2 - +15	+4.0	-9.5 - +7	+0.8

* Group I Patients observed while using Formula A, unmodified Dexedrine and a placebo.
Group II Patients observed while using Formula A and unmodified Dexedrine.
Group III Patients observed while using Formula A and a placebo.
Group IV Patients observed while using unmodified Dexedrine and a placebo.

TABLE III

INCIDENCE OF SIDE EFFECTS NOTED WITH THERAPEUTIC DOSES OF FORMULA A, UNMODIFIED DEXEDRINE, AND A PLACEBO

	Formula A	Unmodified Dexedrine	Placebo
Total No. of Patients	73	61	64
Character and Frequency of Side Effects			
Epigastric Distress	6	6	3
Nervousness	5	5	1
Insomnia	1	2	1
Dizziness	1	1	0
Headache	1	0	0
Palpitation	0	2	2
Total	14	10	7
No. of Patients with Multiple Symptoms	4*	5**	1*
Total No. of Patients with Side Effects	10 (13%)	9 (14%)	6 (9%)

* No individual in these groups displayed more than 2 symptoms.

** Consists of 2 patients displaying 3 symptoms each and 3 patients with 2 symptoms each.

and determinations of blood count, basal metabolic rate, and urinalysis on a representative group of subjects who were observed while on more than one regime showed no significant effect of either of these medications upon the results of such determinations.

III. SIDE EFFECTS (TABLE III).

At the time of return visits, each subject was questioned as to any untoward symptom which may have developed in the interim. The incidence of side effects was surprisingly low. Epigastric distress was the symptom observed most frequently. Increased nervousness was the next most frequently observed symptom. Insomnia occurred very infrequently. It is interesting to note the incidence of side effects when a placebo was taken, and how closely the character of these symptoms paralleled those observed when one of the Dexedrine preparations was used.

In no instance was the severity of any side effect such as to necessitate discontinuance of the medication.

The results of this experiment gave satisfactory answers to two of the problems this study attempted to solve. It proved that a timed-disintegration capsule of Dexedrine taken once daily was at least as effective as an equal total daily dosage of unmodified Dexedrine in curbing the appetite, and that no increase of undesirable side effects ensued by maintaining a sustained therapeutic level of the drug during the course of the day. However, it was felt that some improvement could be made in the composition of the sustained-release capsule both as to the type of coating used, and the dis-

tribution of the dosages of Dexedrine. Several of the patients complained of hunger, especially in the late afternoon, while using Formula A.

FORMULA C

Formula C was similar in principle to Formula A in that individual pellets of Dexedrine were covered with coatings of variable weight and thickness. The coating, however, was different from that employed in Formula A, and the total contents of the capsule consisted of 20 mg. of Dexedrine. It was hoped the addition of another 5 mg. of Dexedrine would eliminate the afternoon hunger of which some of the patients complained while using Formula A.

MATERIALS AND METHODS

Since the superiority of Dexedrine over a placebo had been established, Formula C was compared only with unmodified Dexedrine, 5 mg. three times daily. The same procedure as was used previously was again employed, i.e., insofar as possible, each subject was observed on a course of Formula C and unmodified Dexedrine, thus serving as her own control. The diet was similar to that used previously. Return visits were made every second week. The capsules were again supplied in different colors so as to eliminate the patients' knowing when a change in medication was made.

Since it had been established that Dexedrine preparations had no significant effect upon pulse rate, blood pressure, urinalysis, blood count and basal metabolic rate, comparative studies of these findings were not repeated.

TABLE IV

COMPARISON OF WEIGHT LOSS ATTAINED WITH UNMODIFIED DEXEDRINE AND FORMULA C

No. of Subjects	No. of trials	Unmodified Dexedrine		Formula C	
		Average Time Observed (weeks)	Average Weight Change (lbs. per week)	No. of trials	Average Time Observed (weeks)
42	57	7	-1.1	49	6.8
23				23	6.7
Average of all trials				72	6.8
					-1.3
					-1.8
					-1.4

TABLE V
SIDE EFFECTS OF THERAPEUTIC DOSES OF DEXEDRINE FORMULA C
AND UNMODIFIED DEXEDRINE

	Unmodified Dexedrine	Formula C
Total No. of Subjects	42	65
Character and Frequency of Side Effects		
Nervousness	6	4
Dizziness	2	8
Constipation	2	7
Indigestion and Gas	3	6
Headache	1	5
Total	14	30
No. of Patients with Multiple Symptoms	5*	9**
Total No. of Patients with Side Effects	9 (21%)	18 (28%)

* No patient in this group displayed more than 2 symptoms.

** Consists of 3 patients displaying 3 symptoms each, and 6 patients with 2 symptoms each.

A total of 65 patients was adequately followed. Of these, 42 were observed while on one or more courses of each of the medications. Four of these 42 had 2 trials with each drug, 5 were observed during 2 trials of unmodified Dexedrine and 1 of Formula C, and 3 were observed during 1 trial of unmodified Dexedrine and 2 of Formula C. This resulted in 51 trials using unmodified Dexedrine and 49 trials using Formula C. Of the 42 patients who were observed while alternately taking unmodified Dexedrine and Formula C, 24 received unmodified Dexedrine, and 18 received Formula C initially. Twenty-three subjects were observed while using Formula C only. Since considerable information had already been collected as regards unmodified Dexedrine, data on subjects who were observed only while using unmodified Dexedrine were not included in the final tabulations.

All the 65 subjects were women. Their average age was 41 years, average height 63 inches, and average initial weight 209½ lbs. The deviation of weight from standard was plus 55%.

RESULTS

I. Effects Upon Weight Loss (Table IV).

There was no significant difference in the averaged rate of weight loss in the 42 subjects who were observed while taking each of the two medications. The length of time of observation while on each of the medications was approximately the same. It is also interesting to note that the rate of weight loss while using unmodified Dexedrine was identical with that observed in the earlier study. For those 23 subjects observed only while using Formula C, the average weekly weight loss was somewhat higher. Since we have previously noted that patients usually lose weight more rapidly at the outset, (3) and all these 23 subjects received Formula C as the initial medication, the average weekly weight loss for those patients who received either unmodified Dexedrine or Formula C as the initial medication was calculated. For the 24 patients who received unmodified Dexedrine initially, the average weekly weight loss was 1.5 lbs., and for those 18 who received Formula C initially, the average weekly weight loss was 1.6 lbs., both somewhat higher than the total average.

II. SIDE EFFECTS (TABLE V).

Each subject was questioned regarding any untoward symptoms at each return visit. The relative incidence of

side effects while using unmodified Dexedrine was similar to that found previously. However, there was a considerable increase in the incidence of side effects with Formula C. The reason for this increased incidence of side effects is not clear, but the possibility of this being caused by the larger total daily dosage of Dexedrine in Formula C is suggested.

During the course of this study, an assay of the coatings to determine release time was made. The pellets were made with a radio-opaque nucleus to give well defined contrast in flat abdominal films. On the basis of results obtained by the procedure (the complete details of which are to be reported elsewhere (14)) a new sustained-release capsule formula was determined which, it was believed, would yield the optimal utilization of the Dexedrine. This capsule (Formula J) is the one that is now commercially available.* It contained the same amount of Dexedrine as Formula A (15 mg.) but the resistant coatings were applied in different percentages; this permitted the medication to be more efficiently and evenly released. X-ray pellet counts done on 3 individuals, revealed that Formula J permitted a gradual release of the drug over a span of 8 to 10 hours. It was estimated that the therapeutic effect of Dexedrine would last for approximately 12 hours.

FORMULA J (DEXEDRINE SPANSULES)

In order to confirm our theoretical findings, Formula J was given a clinical trial as an anorexigenic agent. Patients attending the Obesity Clinic at the Welfare Island Dispensary were again used as subjects. A total of 31 patients was observed. The numbers of old and new patients were about evenly distributed. Since the results using unmodified Dexedrine were remarkably constant in the preceding 2 studies, it was not felt necessary to obtain additional data on unmodified Dexedrine. Con-

* Dexedrine Spansule, Smith, Kline & French Laboratories.

TABLE VI
AVERAGED DATA FOR 31 SUBJECTS WHO RECEIVED
FORMULA J*

Age	42 years
Height	63½ inches
Initial weight	203 lbs.
Time observed	5.5 weeks
Weight loss (lbs. per week)	1.3 lbs.

* Dexedrine Spansule sustained-release capsule

TABLE VII

SIDE EFFECTS NOTED WHILE USING FORMULA J	
Total No. of Subjects	31
Character and Frequency of Side Effects	
Constipation	3
Dizziness	3
Epigastric Distress	2
Nausea and Vomiting	1
Insomnia	1
Total	10
No. of Patients with Multiple Symptoms	4*
Total No. of Patients with Side Effects	5 (16%)

* Consists of 1 patient displaying 3 symptoms and 3 patients with 2 symptoms each.

sequently, only the results obtained while using Formula J were observed. All 31 subjects were females. Their average age was 42 years, average height 63½ inches and average weight 203 lbs. The deviation of weight from standard was plus 50%. The same diet as previously described was maintained.

RESULTS

(Table VI)

The average weekly weight loss was similar to that observed when any of the other Dexedrine preparations were used. However, the side effects were considerably less than those observed with Formula C.

Of all the sustained-release capsules studied, Formula J appeared to afford the most efficient and economical use of the Dexedrine with a minimum of side effects.

DISCUSSION AND CONCLUSIONS

As stated above, all of the subjects in the series of experiments were out-patients at a large municipal hospital clinic. Cooperation as far as adherence to dietary instructions was far from ideal for both intellectual and economic reasons. Paradoxically, this could be considered an advantage in a study of this type. Had the diet been scrupulously observed, it is obvious that since all of the patients in all of the studies received the same dietary prescription, the rate of weight loss should have been the same no matter what medication was employed. Since there was a significant difference in the rate of weight loss when any of the Dexedrine preparations were used over that observed when a placebo was used, it seems reasonable to assume that this difference was caused by an anorexigenic effect of Dexedrine which caused less deviation from the diet, since no change in other vital functions could be demonstrated.

It has been our experience that subjective impressions of the anorexigenic effect of medications are of dubious reliability. With a group such as this, the average weekly weight loss supplied a reliable objective measurement of the anorexigenic effect of the medications under investigation. The objectivity is further enhanced by the technic of making each subject her own control, and making the appearance of the medication such that the patient at no time could know which preparation was being employed, or when a change was made.

Although the accuracy of requested information regarding subjective interpretations of the effects of the medications is questionable, we were impressed by volunteered comments which favored the timed-disintegration capsules. Remarks such as "I did not feel quite

so uncomfortable from hunger this time," were not infrequent.

The results of these studies confirm the frequently noted observation that Dexedrine is an effective and safe anorexigenic agent. When this medication is prepared so that the entire daily dose is contained in a single capsule, each granule coated so as to allow gradual absorption during the day, its anorexigenic effect is comparable to that observed when unmodified Dexedrine is administered in divided dosage. The advantages of a preparation that needs to be taken but once daily are obvious. It is also our impression that by maintaining a continuous anorexigenic effect, such a preparation is peculiarly valuable in "nibblers." Such a problem exists very frequently with busy housewives, who say they do not have the time to eat regular meals, but "nibble" all day.

SUMMARY

A new type of Dexedrine preparation ("Spansule" sustained-release capsules) which allows a gradual release of the drug and thus maintains a sustained therapeutic effect throughout the day has been investigated. It has been determined that:

1. Sustained-release capsules of Dexedrine are as effective an anorexigenic agent as unmodified Dexedrine taken in divided dosage.
2. There is no increase in the incidence of undesirable side effects caused by maintaining a sustained drug effect throughout the day.

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AN OBSERVATION ON THE INFLUENCE OF TAPEWORM INFESTATION IN A DOG ON THE SECRETION OF INTESTINAL JUICE

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IN THE COURSE of our experiments on the secretion of intestinal juice under the influence of various pharmacological agents some observations were made on the secretion of *succus entericus* in a dog accidentally infested by tapeworm (*Taenia multiceps*). It is known since the observations of Weinland (1903) (8) that certain intestinal parasites (Ascarides) produce anti-peptic and antitryptic inhibitory substances to protect themselves against the respective ferments of the host. Mendel and Blood (1910) (6), Harned and Nash (1932) (4), Collier (1941) (1) came to similar conclusions. Vegetable proteases, like papain and ficin can digest the living parasites because they have not the respective inhibitory factors (Robbins, 1932) (7). Only recently Harland, Humble and Mann (1950) (2) describing an infestation of a patient by a tape-worm, *Diphyllobothrium latum*, a fish unsegmented worm, reported the presence of histamine fast achlorhydria and that hydrochloric acid did not return to the gastric juice when the worm was expelled. Hernberg (1947) (3) found the same phenomenon and reported that even when hydrochloric acid returns, the acidity is still below normal and there is a reduced secretion of gastric juice in response to histamine. Hernberg infers from this fact that anemia produced by tapeworm occurs in those with a constitutionally defective gastric secretion; the mechanism of this action, however, is obscure.

EXPERIMENTAL

Our observations were made on the dog with a Thiry-Vella fistula and the intestinal juice was collected under the influence of various secretagogues. Mostly histamine and substances acting possibly by the liberation of histamine in the body such as alcohol, were used as the pharmacological stimuli of intestinal secretion. In some experiments also carbaminoylcholine was employed. The intestinal juice was collected from a Thiry-Vella fistula of the dog. In preparing a Thiry-Vella fistula a laparotomy was made under aseptic conditions, the upper part of the jejunum isolated and a loop about 30 cm long was fixed on both sides of the abdominal wall. By this means the loop retained its normal blood and nervous supply but was disconnected from the main intestinal canal. The secreted juice was collected from the both ends of the intestinal loop. The upper part of the jejunum was chosen because the juice secreted in this part of the intestine has the greatest ferment activity in man and in animals.

The intestinal juice was examined for its activity immediately after withdrawal. In order to compare this activity in various stages of our experiments the concentration of the inverting ferment, saccharase,

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was determined polarimetrically, by measuring the amount of inversion produced in 24 hours at 38° C by 0.25 cc of the juice acting on 2 Gm of saccharose in 50 cc of phosphate buffer solution at pH 6, which was found to be the optimum pH for the invertase of the intestinal juice. A few drops of toluene was added as preservative. For each sample of juice the same conditions of temperature, time of inversion, pH etc. were observed.

The observations were made:

- on a normal dog with a permanent Thiry-Vella fistula,
- on the same dog during the period of infestation by a tapeworm (*Taenia multiceps*),
- on the same dog after the expulsion of the head of the worm and disappearance of the segments from the faeces.

The experiments shown in the Tables were made every 2 to 4 days.

RESULTS

a) Normal response.

Histamine produces secretion of the intestinal juice in a normal dog with a Thiry-Vella fistula, starting 1 to 3 minutes after the subcutaneous injection of this substance and continuing for about 20 minutes. The amount of juice varies, depending on the length of the loop and the dose of histamine. The dose of histamine base used as stimulant of intestinal secretion in all our experiments was 2 mg.

In these experiments the intestinal juice was collected from both ends of the fixed loop and its exact volume was measured. The juice was then ground with broken glass to liberate the intracellular saccharase, which is an endoferment, and added to the saccharase-buffer solution. Polarimetric determinations were then made immediately and 24 hours after incubation of a portion of the solution which had been clarified by centrifugation. The secretion of intestinal juice started 1 to 3 minutes after the injection of histamine and the average amount of juice secreted during 20 minutes of observation was 1.86 cc (maximal amount 3.55 cc, minimal 0.65 cc). The average amount of inversion produced per hour during 24 hours of incubation was 4 minutes and 56 seconds (rotation maxima 6°75', minima 3 minutes per hour).

In Table I the results of six such experiments are illustrated.

b) Response during infestation.

At the end of the sixth week of observation the dog was found infested by the tapeworm (*Taenia multiceps**). Many segments of the worm were found ev-

*The identification of *Taenia multiceps* was kindly made by Professor Nagati and Dr. Ragab.

EFFECT OF TAPEWORM ON INTESTINAL JUICE

TABLE I

The volume and character of intestinal juice secreted in response to histamine injection. The activity of invertase is given in terms of its power to invert a 4% solution of saccharose.

No. of experiments	Onset of secretion after histamine	Amount of juice	Appearance	Inversion per hour
1	3 minutes	0.65 cc	Clear, sticky	3' 75''
2	2½ minutes	0.75 cc	Clear,	3' 00''
3	2½ minutes	3.55 cc	Clear,	5' 80''
4	½ minute	3.00 cc	Clear	6' 75''
5	2 minutes	2.00 cc	Clear, some flocculations	3' 30''
6	2 minutes	1.00 cc	Clear, some flocculations	4' 79''
	Average	1.86 cc		4' 56''

TABLE II

The volume and character of intestinal juice secreted in response to histamine injection during tapeworm infestation. The activity of invertase is given in terms of its power to invert a 4% solution of saccharose.

No. of experiments	Onset of secretion after histamine	Amount of juice	Appearance	Inversion per hour
1	1 minute	0.7 cc	Opaque, little flocculations	0' 00''
2	1 minute	2.2 cc	Turbid, little flocculations	2' 25''
3	2 minutes	0.3 cc	Clear, transpar.	0' 00''
4	3 minutes	0.07 cc	Clear, transpar.	0' 00''
5	1½ minutes	0.65 cc	Clear, transpar.	6' 87''
6	1½ minutes	0.30 cc	Translucent	3' 30''
7	17 minutes	two drops	Clear	0' 00''
8	15 minutes	one drop	Sticky	17' 15''

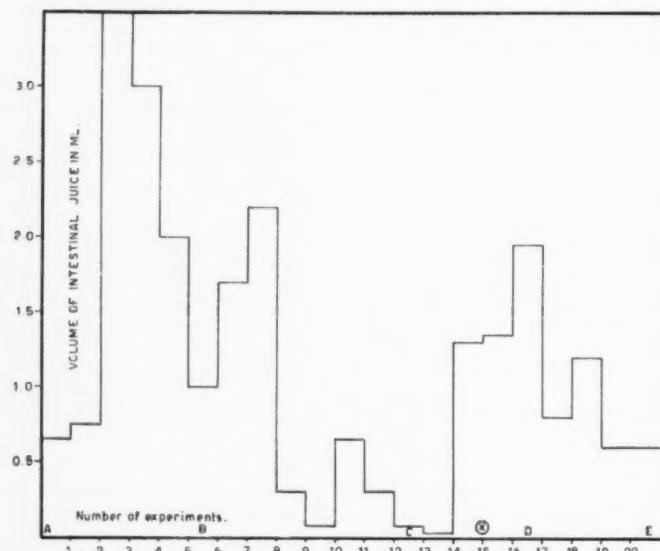


Fig. 1. The figure shows the amount of intestinal juice in cc collected during 20 minutes of observation from a dog with a permanent Thiry-Vella fistula after injection of 2 mg. of histamine base. The juice was collected before, during the infestation by tapeworm (*Taenia multiceps*) and after the expulsion of the head of the worm. In experiments 17 to 20 alcohol was used as secretagogue.

A - B (Exper. 1 - 6)—period before infestation. Normal response.

B - C (Exper. 7 - 13)—period of infestation. The amount of the secreted juice greatly diminished.

C - D (Exper. 14 - 16)—period after the expulsion of the head of *Taenia multiceps*.

D - E (Exper. 17 - 20)—two weeks later. Response to intravenous injection of alcohol 30 p.c.

⊕ —injection of doryl, 6 micrograms per Kg. body weight.

TABLE III

The volume and character of intestinal juice secreted in response to histamine injection after the expulsion of the head of *Taenia multiceps*. The activity of invertase is given in terms of its power to invert a 4% saccharose solution.

No. of experiments	Onset of secretion after histamine	Amount of juice	Appearance	Inversion per hour
1	6 minutes	1.25 cc	Clear	4' 58"
2	2 minutes	1.30 cc	Opaque, sticky	3' 75"
3	3 minutes	2.20 cc	Turbid, flocculations	13' 75"

TABLE IV

The volume and character of intestinal juice secreted in response to the intravenous injection of 10 cc of ethyl alcohol (30 p.e.) in a dog with a permanent Thiry-Vella fistula after complete cure from parasitic infestation by tapeworm (*Taenia multiceps*). The activity of invertase is given in terms of its power to invert a 4% solution of saccharose.

No. of experiments	Onset of secretion after alcohol injection	Amount of juice	Appearance	Inversion per hour
1	4 minutes	0.8 cc	Turbid, flocculations	4' 58"
2	4 minutes	1.0 cc	Turbid, flocculations	8' 33"
3	3 minutes	0.5 cc	Dense flocculations	12' 50"

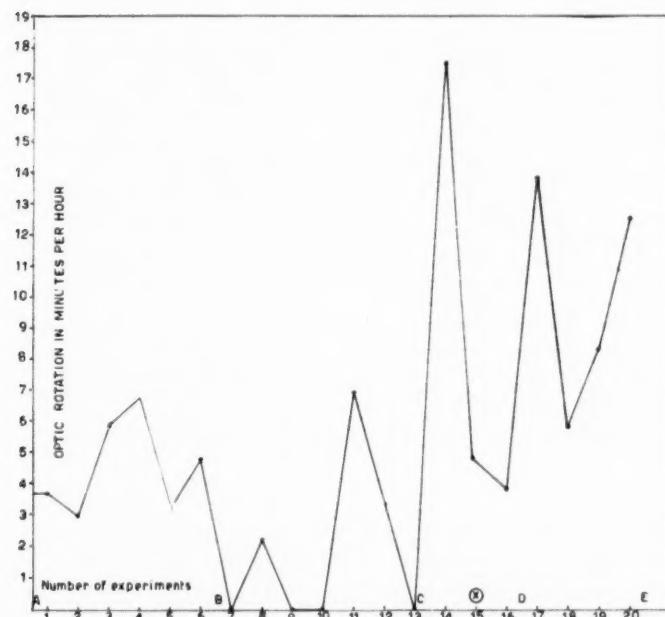


Fig. II. The figure shows the inverting power measured by optic rotation in degrees (minutes and seconds) per hour of intestinal juice collected during 20 minutes observation from a dog with a permanent Thiry-Vella fistula after injection of 2 mg. histamine base. The juice was collected before, during the infestation by tapeworm (*M. multiceps*) and after the expulsion of the head of the worm. In experiments 17 - 20 (D - E) alcohol was used as secretagogue.

A - B (Exper. 1 - 6)—period before infestation. Normal response.
B - C (Exper. 7 - 13)—period of infestation. The activity of invertase is greatly diminished.

C - D (Exper. 14 - 16)—period after the expulsion of the head of *M. multiceps*.

D - E (Exper. 17 - 20)—Two weeks later. Response to intravenous injection of alcohol 30 p.e.

⊕—injection of doryl, 6 micrograms per Kg. body weight.

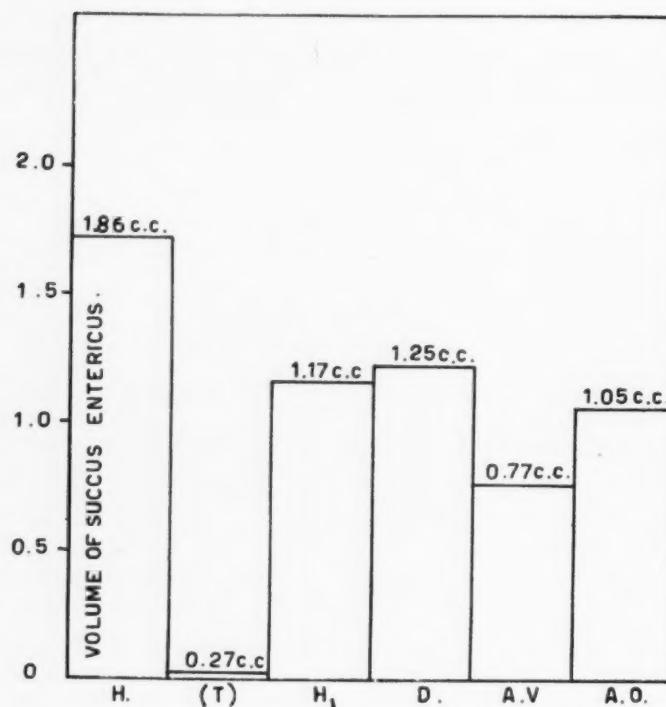


Fig. III. The figure shows the average amount of intestinal juice in cc collected during 20 minutes of observation from a dog with a Thiry-Vella fistula after injection in histamine, doryl and alcohol. The juice was collected before, during the infestation by tapeworm (*Taenia multiceps*) and after the expulsion of the worm.

H—volume of succus entericus in cc collected from the fistula before the infestation by tapeworm, under the influence of histamine.

T—volume of succus entericus collected from the fistula during the period of infestation of the dog by *Taenia multiceps*. Histamine was used as secretagogue.

H₁—volume of succus entericus collected from the fistula after the expulsion of the head of the tapeworm. Histamine was used as stimulant of secretion of succus entericus.

D—the same as H₁—doryl was used as secretagogue.

A.V.—volume of succus entericus in cc collected from the fistula two weeks after the expulsion of the head of the tapeworm (*Taenia multiceps*). The secretion of succus entericus was produced by intravenous injection of 10 cc of 30 p.c. ethyl alcohol.

A.O.—the same as above. The secretion of succus entericus was produced by oral administration of 7 p.c. of alcohol.

ery day in the faeces. The faeces were abundant and semisolid, occasionally with mucus.

The worm—*Taenia multiceps*—develops in the brain and spinal cord of sheep, cattle, horse and goat. It has been found in man too. The embryos after hatching in the intestine are carried by the blood stream to other parts of the body. Those reaching the central nervous system develop, others die. The cysts in the brain wander about before settling and are fully developed in 7 to 8 months causing lesions according to the site of injury in the central nervous system. The final host (dog, fox, jackal) becomes infested on eating the cysts of *Taenia* in the brain tissue. Then in the intestine the small scoleces (heads) of the worm get invaginated and nearly all of them produce adult tape-worm.

We observed the secretion of intestinal juice during the period of infestation by *Taenia multiceps*. It seemed that infestation with this parasite had markedly altered the usual response of the dog to histamine injection: the volume of the intestinal juice was diminished, the invertase activity inhibited and the onset of the secretion in some experiments was delayed. These effects are illustrated in Table II.

After the experiment No. 7 the worm 45 cm. long was expelled, the presence of head with rostellum and hooks and suckers was determined under the microscope.

It is clear from the data presented in Table II that infestation by the worm *Taenia multiceps* produced a marked diminution of the amount of intestinal juice secreted under the influence of histamine. The activity

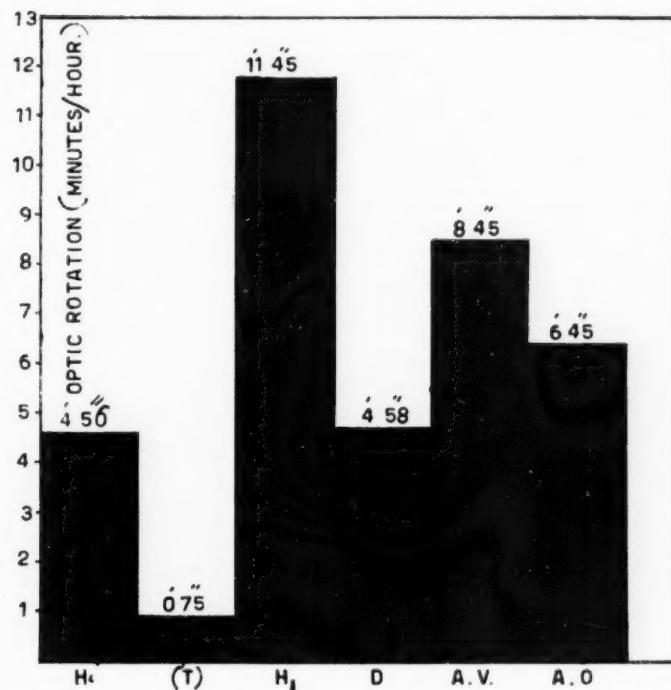


Fig. IV. The figure shows the average inverting power of sucrase measured by optic rotation in degrees (minutes, seconds) per hour. Intestinal juice was collected during 20 minutes from a dog with a Thiry-Vella fistula after injection of histamine, doryl and alcohol. The juice was collected before, during the infestation by tapeworm (*M. multiceps*) and after the expulsion of the head of the worm.

H—invertase activity (optic rotation in minutes per hour) of succus entericus collected before infestation. Histamine was used as a stimulant of secretion of intestinal juice.

(T)—optic rotation in minutes per hour produced by succus entericus collected during period of infestation of the dog by *M. multiceps*. Histamine was used as a stimulant of the secretion.

H₁—the same after the expulsion of the head of the worm. Histamine was used as a stimulant of secretion.

D—the same after the expulsion of the head of the worm. Doryl was used as a stimulant.

A.V.—invertase activity of succus entericus collected two weeks after the expulsion of the head of the worm. The secretion of succus entericus was obtained by the intravenous injection of 30 p.c. of ethyl alcohol.

A.O.—the same. The secretion of succus entericus was obtained by oral administration of 7 p.c. of ethyl alcohol.

of invertase was also greatly inhibited, in some experiments down to zero. In experiment No. 5 and 6 there was a spontaneous increase of the activity of invertase; it is known, however, that as regards the symptoms of anemia produced by *Diphyllobothrium latum*, spontaneous remissions also occur without the worm being expelled (Harland, Humble and Mann, 1950). It is very probable that a similar phenomenon occurred in our case, the strength of intoxication being diminished for a few days despite the actual presence of the worm.

c) *Response after the expulsion of the whole worm.*

The following day after the expulsion of the tapeworm there was a rise in the degree of invertase activity of the intestinal juice although its volume was still very small (one drop). After two days both the

volume and enzymatic activity returned almost to normal levels as may be seen from Table III and Figures I and II.

In order to control the secretory response and to examine the amount and enzymatic activity of the intestinal juice of the dog cured from the infestation by tapeworm we studied the influence of alcohol introduced by mouth or by intravenous injection on the secretion and properties of intestinal juice. We found that ethyl alcohol introduced by mouth in 7 p.c. solution or injected intravenously in 30 p.c. solution produces a secretion of intestinal juice very similar to that produced by histamine. (5) (5a). In this case some experiments were performed with alcohol introduced by mouth or injected intravenously two weeks after the complete cure of the dog from *Taenia* infestation and

they showed the normal response to this stimulus, as shown in Table IV and Figures No. III and IV.

The oral introduction of ethyl alcohol in a 7 p.c. solution provoked similar effects.

In Figures III and IV the average responses of the secretion of the intestinal juice to the various pharmacological stimuli used during this investigation are shown.

DISCUSSION

Observations made on the dog with a permanent Thiry-Vella fistula showed that infestation by tapeworm (*Taenia multiceps*) provoked a diminution in the amount of the intestinal juice secreted under the influence of histamine. The activity of invertase was inhibited and in some experiments the onset of the secretion was delayed. The results obtained show that the inhibitory effects of tapeworm infestation were probably due to the general action of a toxic substance resulting from the presence of the worm in the intestines. The isolated loop of jejunum being absolutely free from the presence of the worm it is clear that the effect is the result of a general intoxication. The inhibitory effects, however, were interrupted by a short period of remission in which the intestinal juice almost regained its normal character. These fluctuations may be due to diminution in the absorption of the toxic agent for short periods or to the action of a protective substance in the body.

The infested dog presented not only the usual signs of diarrhoea and the presence of mucus in the feces which contained a large number of worm-segments

but its general health was also affected (loss of weight, weakness, etc.). After the expulsion of the head of the worm all these symptoms disappeared together with the reappearance and maintenance of the normal secretory conditions of intestinal juice.

CONCLUSION

The infestation of a dog, having a permanent Thiry-Vella fistula, with a tapeworm (*Taenia multiceps*) provoked a marked diminution in the amount of the secreted juice under the influence of histamine. The invertase activity of this juice was also inhibited. The expulsion of the head of the worm and the consecutive cure of the dog produced a complete recovery of the secretion of intestinal juice and restored its normal enzymatic activity.

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MULTIPLE PERFORATIONS OCCURRING DURING THE TREATMENT OF ULCERATIVE COLITIS WITH ACTH

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RECENTLY (1) three cases of bowel perforation and peritonitis occurring during the treatment of ulcerative colitis with corticotropin were reported. Previous instances of similar occurrences are sparse (2). It is felt, therefore, that reports of additional cases, such as that which follows, are indicated if a proper evaluation of the place of corticosteroids in the treatment of this disease is to be obtained.

CASE REPORT

Mrs. G. H., a 32-year-old white female was admitted to Mercer Hospital October 11, 1952, complaining of bouts of lower abdominal pain and diarrhea of six years' duration.

Except for scarlet fever in childhood, her past medical history was negative. Her father died of carcinoma of the stomach and her mother was a diabetic. The patient was one of six children; she married at 24 years

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Submitted March 20, 1953.

of age, and had two normal pregnancies. Six years prior to admission and two years after marriage she began to have bouts of abdominal pain and diarrhea, for which she was hospitalized elsewhere. The diarrhea consisted of ten to fifteen loose stools per day, containing mucus and streaks of blood. Two weeks of hospitalization resulted in symptomatic improvement and a clinical diagnosis of ulcerative colitis. Therefore, although she was under close medical supervision, she continued to have bouts of colitis until her second pregnancy (two years after onset of diarrhea), during which she was completely well and so remained until the death of her father, nine months before admission. She then began to have watery diarrhea without blood. This persisted in spite of symptomatic and sulfonamide therapy, and for four weeks prior to admission the stools numbered ten per day. The patient lost fourteen pounds. A trial of aureomycin the week before admission resulted only in nausea. A few days before admission, fever and chills appeared, and hospitalization was advised.

Physical Examination on admission revealed a thin,

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pale, dehydrated white female with evidence of weight loss. The tongue was slightly coated. There was tenderness over the lower abdomen and in the left upper quadrant. Peristalsis was hyperactive. Sigmoidoscopy revealed numerous bleeding points in the mucous membrane of the rectosigmoid, and there was polypoid hyperplasia between ulcerated areas of edematous mucosa. Blood pressure was 110/86, pulse 96, temperature normal.

It was decided to give the patient a trial of conservative therapy; hence she received bismuth salts, kaolin, phenobarbital, belladonna and nux vomica by mouth, liver extract, fluids and blood parenterally. During this time her stools numbered nine to fifteen per day and contained gross blood; her temperature varied daily from 99.6° to 103.8°. After one week, ACTH was started, 10 mgms. of ACTHAR gel being given intramuscularly daily; the patient was also placed on penicillin, streptomycin, and potassium citrate. Within 24 hours, the temperature was normal, and after 48 hours the pulse was 80.

The stools decreased in number from 10-15 to 5-9 per day, and the patient's appetite and mental outlook improved. The leukocyte count, which on admission had been 18,900 with 84% neutrophils, dropped to 9,250

on the second day of ACTH therapy. No eosinophil counts were made, but it was felt that a clinical response was in progress. (See Fig. A.)

On the fourth day of ACTH therapy, the patient began to complain of continuous sharp pain in the lower right quadrant, requiring Demerol. It was noted that the abdomen seemed slightly distended. As the patient did not now take adequate fluids because of the abdominal pain, 20 mgms. of ACTH intravenously in 1000 cc. of glucose solution was substituted for the ACTHAR gel. The pain continued over the next eight days and required occasional narcotics. The temperature remained normal, however, and the stools continued at 5-6 per day. They were dark-greenish-brown in color, and no gross blood was noted. The rectum became very irritated and tender.

On the twelfth day of ACTH therapy the patient could not eat at all, and was unable to lie flat. Her stomach was irrigated with bicarbonate solution, and a small (2 ounce) barium meal given. ACTH was discontinued.

The progress of this meal was followed for the next 48 hours, and the roentgenologist, Doctor Paul Mains, reported that the films showed very much delayed emptying of the stomach and retarded passage through

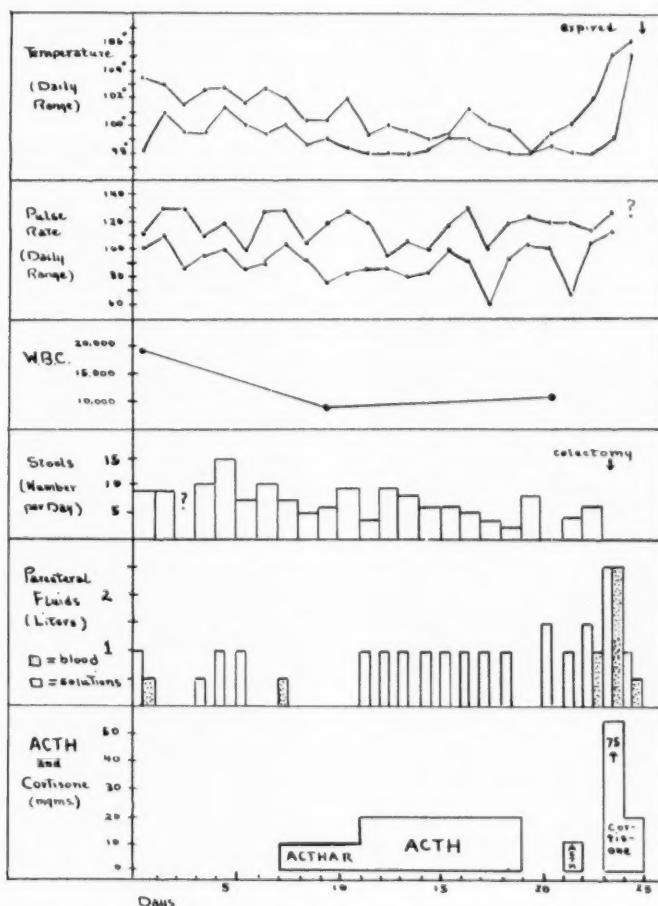


Figure A. Clinical data in Case G.H.

the small bowel, the barium never going beyond a point in the mid-ileum. There was moderate dilatation of small bowel down to and beyond this point.

The condition of the patient on this, the twenty-first hospital day and second day after discontinuing a twelve-day course of ACTH, was poor. Her pulse was rapid, and the stools numbered 4-6 per day; she complained constantly of abdominal pain, and was unretentive. It was necessary to insert a Levine tube and employ continuous suction. There was still a normal temperature, however, and the leukocyte count numbered 10,750 with 77% neutrophils. The patient was given intravenous fluids and blood, and the antibiotics were continued. After two days of decompression, she seemed improved, and the tube was removed; however, severe abdominal pain followed, the tube had to be replaced, and many loose, bloody stools ensued. Her temperature rose to 102°, and she appeared very toxic. Another x-ray of the abdomen showed that there had been no progress of the barium through the small bowel, six days after its oral administration. It was decided that surgery was indicated, with fear that unrecognized perforation and ileus had occurred.

OPERATIVE SUMMARY

Through a long left rectus incision, the abdomen was explored. Several loops of distended proximal ileum presented, and it was found that the terminal ileum was adherent at several points to the transverse colon; the descending and sigmoid portions of the colon were adherent to the parietal peritoneum. Dissection of the

points of adherence in the transverse colon revealed three areas of perforation with small abscess formations. There had been no generalized peritonitis and there was no free fluid in the peritoneal cavity.

The entire colon was extremely friable. Instead, therefore, of attempting to plicate the perforations, it was elected to do a sub-total colectomy and a right lower quadrant ileostomy (for which the ileum proximal to that adhering to the transverse colon was used) and a mucous fistula, utilizing the lower sigmoid colon. During the procedure the patient's condition was very poor, blood pressure dropping to unobtainable levels despite the administration of five pints of whole blood, 75 mgms. of cortisone, and Vasoxyl Rx.

The day following surgery the patient was conscious but still in profound shock, with no pulse nor blood pressure obtainable. She received Cortone^R, whole blood, Levaphed^R, and glucose solution but she lapsed into a coma and expired twenty-six hours following operation, on the twenty-fifth hospital day. An autopsy could not be obtained.

Pathological Examination of the colon, by Doctor Thomas K. Rathmell, showed two perforations, necrotic in appearance, and covered on their serosal surface with a yellowish plastic exudate. The mucosa of the bowel was irregularly ulcerated and greyish, with a hyperemic, edematous aspect. *Microscopic Examination* showed an edematous wall with multiple areas of acute and sub-acute ulceration of the mucosa. (See Fig. 1). The edges of the ulcers were undermined in



Fig. 1. Microscopic appearance of the colon in Case G. H. showing an area of sub-acute mucosal ulceration at A, extending into the muscularis.

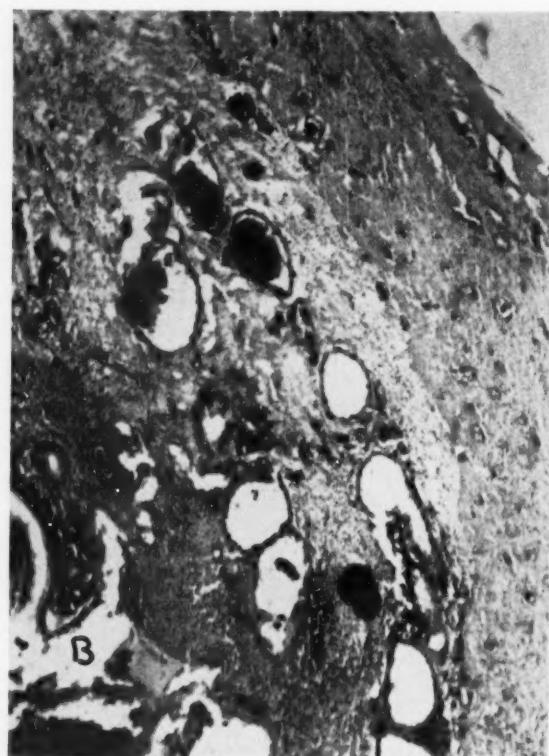


Fig. 2. Microscopic appearance of the colon in Case G. H. showing acute mucosal ulceration at B with underlying hyperemia and edema of the sub-mucosa.

varying stages from simple erosion to extension into the muscular layer and serosa. There was vascular hyperemia and hemorrhagic thromboses in the tissue in the ulcer beds (See Fig. 2) with either polymorphonuclear exudate or focal abscesses into the bowel wall. In some areas the serosa showed acute and sub-acute inflammatory exudate. (See Fig. 3, 4.)

Final Diagnosis was "acute ulcerative colitis, extensive, with areas of complete dissolution of the bowel wall and multiple perforations."

COMMENT

Discussions of the rationale and usefulness of the corticosteroids in the treatment of ulcerative colitis have been adequately presented by others (1, 3, 4, 5). Reports of failures and relapses are not uncommon (6), but the general tendency at present in the management of chronic ulcerative colitis is to institute hormonal therapy, where not contraindicated, in the hope that a long-term clinical remission may be obtained. Some of the more seriously ill patients are those in whom the most dramatic responses have occurred, which, while temporary, have allowed surgery to be carried out (2).

In view, however, of the masking action of the corticosteroids on the signs and symptoms of acute inflammation, and their ability to retard wound healing, it is questioned whether they should not be employed with more caution in a condition, the prominent features of which are ulceration and inflammation.



Fig. 3. Microscopic appearance of the colo in Case G. H. showing a thick inflammatory exudate overlying an area of mucosal slough.

The case presented here illustrates the hazard of relying on temperature readings and leukocyte counts for proper evaluation of inflammation. The elevated pulse rate on the 19th hospital day, the development of ileus and the exacerbation of abdominal pain should have raised the suspicion of a perforated viscus. The profound shock which developed in the ensuing four days, despite blood and, later, corrective hormone replacement, probably represented severe pituitary and adrenal incompetence following the sudden withdrawal of exogenous pituitary adrenocorticotropin.

Since the initial dose of ACTHAR gel was low, and no eosinophile counts were taken, absolute proof of hormonal influence on the course of events in this case are lacking. However, the acute necrosis of bowel wall observed is compatible with the inhibiting action of ACTH on all manner of tissue repair and resistance, and exceeds that to have been expected from the natural course of acute ulcerative colitis itself.

Therefore, in chronic ulcerative colitis, the use of corticosteroids probably should be reserved as an alternative form of treatment only after other reasonable and practical forms of therapy have been given a fair trial, including adequately supportive psychotherapy. Also, the use of corticosteroids in acute, fulminating cases, should preferably be of short duration, fortified adequately by supportive measures, and followed as soon as possible by surgery, during which the hormonal replacement is maintained until it can be reduced gradually without causing irreversible, profound endocrine imbalance, such as probably occurred in this case.



Fig. 4. Higher magnification of a portion of Figure 3.

SUMMARY

A fatal case of multiple bowel perforations and peritonitis occurring in a 32-year-old white female treated with ACTH during an acute exacerbation of chronic ulcerative colitis is presented. The signs of acute inflammation were partially suppressed, although those of perforation were present. Profound shock attended surgery after withdrawal of the hormone.

The use of corticosteroids in ulcerative colitis is discussed, and certain limitations of its usefulness proposed.

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HYPOPOTASSEMIA DUE TO CARDIOSPASM

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CARDIOSPASM IS a not too infrequent symptom complex most commonly seen in males between the ages of thirty and fifty. Its onset is characterized by episodes of dysphagia, especially involving liquids which, early, show spontaneous remissions but, with time, become progressively more frequent and severe. Whereas the etiology is not certain, the pathologic physiological pattern seems to be a functional obstruction at the esophageal-cardiac junction coupled with forceful, but incompletely effective, esophageal peristalsis. As a result, the thoracic esophagus initially undergoes work hypertrophy but, as the condition progresses, it fails to develop apace and becomes dilated and eventually atonic; in a sense, decompensated.

Theories as to the etiology have remained unproven. Wolf and Almy (1) demonstrated that severe mental stress in a previously symptom-free person could evoke the symptoms of cardiospasm. Others have also championed the psychic aspects and have suggested that neurotic individuals have selected a biologic pattern by which the stomach is normally protected against an irritant and have overly developed this pattern to protect themselves against situations which they "cannot swallow." Faulkner (2) points out that cardiospasm does not occur in happy, well adjusted persons and McMahon et al (3) suggest that the patient with this condition should not only be helped with medications and instrumentation but also with sympathetic understanding of their problems and, eventually, with psychotherapy. According to Hurst, (4) there is an achalasia of the cardiac sphincter; that is, a failure to relax when the esophageal peristaltic wave approaches. Anatomically, there is no musculature suggestive of a sphincter at the esophageal termination but functionally, as noted on gastroscopy, there is a sphincter action. Alvarez (5) and Raffe (6) and Etzel (7) have all suggested that degenerative changes in the intrinsic esophageal plexi may be causative, and the latter

author has demonstrated such histologic changes in Brazilian natives who had lived on grossly deficient diets and who manifested the symptoms of cardiospasm. However mediated, cardiospasm may also be secondary to some other gastrointestinal disorder and it is not uncommonly seen in chronic diseases of the gallbladder, stomach, duodenum and appendix.

The symptomatology mirrors the stage of the functional disturbance. The progressive dysphagia merges into regurgitation and vomiting as the hypertrophic esophagus is unable to propel the food distad and reverse peristalsis supervenes. Xiphoidal pain referred to the neck and jaws is common, and as dilatation progresses, this pain may simulate angina pectoris. Mediastinal pressure, esophagitis and esophageal ulcers have all been known to contribute to the patient's discomfort. In the later stages of cardiospasm, malnutrition, weight loss, anemia, avitaminosis, dehydration and pneumonia, frequently of the aspiration type, evidence the debility that may result.

The diagnosis is generally suggested by the clinical history. Roentgenograms, except in early stages, confirm or establish the diagnosis. Gross dilatation and hypertrophy, as manifested by very active peristalsis, and later, tortuosity of the esophagus are noted. Characteristically, the margins of the constricted portion are smooth and cone down to the cardia. Even in seemingly certain cases, esophagoscopy should be done to exclude carcinoma as a cause of the obstruction as well as to exclude the presence of esophagitis or peptic ulceration.

Dilatation is the treatment of choice. Mercury weighted bougies, as advanced by Hurst, are in our experience, highly satisfactory and much less traumatic than pneumatic or hydrostatic pressure procedures. In the rare instances where dilatation fails, surgery may be necessary. Transthoracic and abdominal esophagogastronomy, esophagoplasty and cervico-dorsal sympathectomy have been done but no adequate series has been compiled to evaluate their relative results.

Recently, Nickerson and Call (8) have obtained excellent results in one case of cardiospasm through

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the parenteral administration of dibenamine, a potent adrenergic blocking agent. This result suggests a causative role of sympathetic over-activity in cardiospasm. Atropine and belladonna have been time-honored drugs in the long-term treatment of cardiospasm. To repeat, psychotherapy, at various levels of intensity, is often necessary.

Heretofore, to our knowledge, there has been no documented case of hypotassemia as a consequence of severe cardiospasm although it has been reported as occurring in other gastrointestinal disorders. The metabolism of potassium has recently been carefully documented from many sources (9-13). We would like to discuss a case of cardiospasm exhibiting marked potassium deficiency in which the other electrolytes were also disturbed but not in the pattern usually seen with potassium deficiency.

CASE

Some five years previously this 58-year-old white male school teacher had first noted sudden emesis of small amounts of food while, or soon after, eating. These episodes occurred suddenly and forcefully and were not associated with nausea or pain but seemed to follow a "contraction" in the epigastric region. Although his appetite had remained good, he began to lose weight because these emeses began to occur with each meal forcing him to eat lesser amounts and softer foods. In this first year he lost approximately 70 pounds before consulting a physician. Roentgenographic studies were made of the upper gastrointestinal tract after which he refused to be hospitalized for observation of a "growth."

He continued as above, steadily becoming weaker and losing an additional 39 pounds, and was not seen again by a physician until November 2, 1950, two days after he had been carried home exhausted and somewhat confused.

During this five year period he had had no intercurrent illnesses until September, 1950, when he had an "afebrile" episode associated with cough, sore throat, rhinitis and chills, lasting a few days. Following this, his family noted a definite increment in his weakness. Other medical history was non-contributory.

For several days after his collapse, he was treated at home with hypertonic glucose solutions in small amounts by another physician until his condition became critical.

He was hospitalized at Mount Sinai Hospital on November 10, 1950, in an emaciated, dehydrated and confused state. His rectal temperature was 100.4° upon admission but immediately rose to and stayed at about 101.5° F. The pulse rate was 90 per minute, weak and regular. The respirations were 32 per minute, and were regular but deep (tachypnea and hypernea). His pupils were round and equal. Crepitant rales were present in both bases. The heart tones were poorly heard. No murmurs were heard. Blood pressure was 150/105. The left upper quadrant was tender; otherwise the entire abdomen was normal. Easily reducible bilateral inguinal herniae were present. Weakness and flaccidity of all the extensor motor groups were pronounced.

Esophagoscopy revealed no intrinsic esophageal pathology, but marked spasm of the lower third was noted.

Penicillin and intravenous fluids were started on admission and with the return of a CO_2 combining power of 32 volumes per cent on November 11, sodium lactate solution was added. The potassium, sodium and chloride levels were also ordered and on November 12, the chlorides (as NaCl) returned as 137 mEq. The total 24 hour urine on the next two days contained 7.54 grams and 10.22 gms. of chlorides respectively in spite of the absence of any oral intake. The total serum proteins were normal but a definite azotemia (75 mg. per cent) was present.

An attempt to pass a Levine tube into the stomach was made, apparently unsuccessfully, for the patient continued to vomit the nourishments given through it.

On November 13th, the laboratory reported the sodium level as 148 mEq/L, potassium as 3.6 mEq/L and the pH as 7.49. On the next day 1.49 grams (20 mEq) of potassium chloride were added to the glucose in water which was given

daily. Saline solution was thought to be contraindicated in view of the normal sodium and high chloride levels already present.

Thereafter, daily examinations of the electrolytes and pH and CO_2 combining power were attempted with replacement therapy given as indicated.

The patient's condition varied with the potassium level. When it was low, he had flaccidity of the extremity musculature but more than slight respiratory distress was never noted even though a bilateral bronchopneumonia was present. The accessory muscles of respiration were not used.

The azotemia continued and although the CO_2 combining power was slightly low, the pH was always on the alkalotic side.

On November 15, the esophagus was dilated by balloon pressure (Dr. M. Guttmann) and remained patent thereafter though a few small bloody emeses occurred shortly after. A Levine tube was easily passed into the stomach and was left in. For about a week following this procedure, the patient had frequent loose and bloody stools daily.

In spite of oral intake of potassium citrate and liquids rich in potassium, the patient could not maintain a satisfactory serum potassium level without daily intravenous replacement which varied from 1.49 grams to 8 gms. of potassium chloride on the 20th of November when smaller doses totaling 18 grams (approximately 250 mEq) in the previous four days had failed to elevate the potassium level from 1.5 mEq/L to normal. Thereafter, the level was satisfactory and, on the 21st, intravenous potassium was discontinued except for one further dose of 1.49 grams on November 25th. Oral potassium was continued throughout in the form of potassium citrate, potassium iodide (for cough), juices and broths. One and a half liters of blood were administered to correct a moderate anemia. Aureomycin in large doses had been added to the penicillin as the chest findings and fever persisted, however, as electrolyte balance was restored and the patient was able to get out of bed into a wheel chair, he began to cough up much mucopurulent material and the temperature and lung findings decreased.

The improvements noted after November 20th were followed by a sharp reduction in the nitrogenous retention to a stable low-grade azotemia. The urinary intake and output had remained satisfactory throughout hospitalization. The outputs varied between 1400 cc. to over 4000 cc. per day. The specific gravity was always low (1.005 to 1.014). The mental confusion cleared with rehydration and replacement therapy and was completely restored on discharge.

We think it would be advisable to attempt an interpretation of some of the findings and to reevaluate the therapy in such a case:

The untreated cardiospasm led to a state of dehydration, starvation and electrolyte losses with consequent general debilitation, susceptibility to infections and sensitivity to changes in the internal environment. These are general terms but are of serious import when considering the pathologic physiology.

For example, we had in this patient an azotemia and a large daily urinary output of low specific gravity. That it was not all due to irreversible renal damage is seen by the return to a lower level with general improvement. Contributing to the azotemia were the increased protein breakdown resulting from a febrile state and from the utilization of body protein in the absence of exogenous food sources and also the resorption of protein products from the gastrointestinal bleeding. That degree of renal damage which was present probably prevented the elaboration of a concentrated urine, however, this is also seen in severe illnesses and in prolonged or severe dehydration and is due to a reduction in glomerular filtration and tubular resorption. In such states there are large amounts of waste products resulting from tissue breakdown and faulty metabolism requiring excretion and in the absence of efficient concentrating ability the kidney compensates by excreting large amounts of diluted urine. These considerations help to

understand the azotemia and polyuria of low specific gravity.

Early electrolyte study revealed a normal sodium, an elevated chloride and a low potassium and CO_2 combining power with a high pH. This relationship is not clearly apparent. Were vomiting the sole cause of the potassium loss, we might also expect decreased chlorides and the same would be expected if the patient were solely in negative potassium balance, especially as we have evidence of increased urinary excretion of chlorides. However, in cardiospasm, the amount of gastric juice lost in the emesis might well be nil and indeed, if any is lost, it may be free of chlorides. The deficiency of potassium resulting from the absence of oral intake of dietary potassium was increased by the continued loss accompanying cellular breakdown and the undetermined amount of gastrointestinal bleeding. The kidneys do not efficiently conserve potassium but rather excrete it obligatorily, hence steady loss without replacement leads to a deficiency.

As potassium is lost in the urine, an attempt to maintain electrolyte equilibrium in the fluid compartments of the body sacrifices chlorides from the extracellular fluids to the urine and retains sodium to balance the rise in extracellular bicarbonate which occurs as a compensatory mechanism in the chloride loss. The net result of the process is a metabolic alkalosis with a rise in both the CO_2 combining power and the pH. Also creating an alkalosis, but causing a decrease in the CO_2 combining power was the hyperventilation as a consequence of a bronchopneumonia, fever and anemia, the latter being increased by the gastrointestinal bleeding. The pH rather than the CO_2 combining power gave the true picture; that of a predominant respiratory alkalosis combined with hypotassemic alkalosis.

Perhaps the high serum chloride level can be explained on the chloride shift from the red blood and tissue cells in response to the loss of CO_2 through the lungs. We had information from the patient that he was achlorhydric and on several occasions aspirations through the Levine tube were alkaline to litmus paper so he apparently lost negligible amounts of chloride through vomiting.

The normal sodium level we ascribe to conservation of sodium by the kidneys in the face of potassium loss. The patient had also received sodium lactate solution just prior to the time blood was drawn for sodium determination.

Truly, an attempt to understand electrolyte changes poses a serious problem for the physician and every attempt should be made to cope with it.

The treatment was mainly intravenous replacement. Normal saline was contraindicated as chloride replacement could have facilitated potassium loss by allowing simultaneous excretion of the two.

In spite of the azotemia, it was decided that protein hydrolysate replacement was necessary for tissue repair. The need for water and glucose requires no comment. Potassium replacement was inadequate at first but it was soon realized that larger doses were required and these were given.

The importance of potassium metabolism is now well recognized but aberrations thereof in a patient are still being overlooked or neglected. In gastrointestinal diseases, medical and surgical, hypotassemia is a constant possibility because of poor intake or increased

losses due to vomiting, diarrhea, intestinal drainage and tissue breakdown. The entity of hypotassemia may manifest itself in several ways from either a clinical or laboratory viewpoint. Of course, serum electrolyte determinations are the first step, however, it is now known that serum potassium levels do not always reflect the cellular concentration which is the important factor. The typical electrolyte picture is that of a hypotassemic hypochloremic alkalosis as mentioned. Decreasing renal function may result from any continuing state of alkalosis and may be the indication of the underlying cause. Similarly, myoneural changes reflected in hypotonia and myocardial changes reflected by changes in the E.C.G. may be present. Variations in other electrolytes, particularly calcium may modify these latter findings. Our patient did not manifest any E.C.G. changes of the type ascribed to hypokalemia and hence, although often of value, this method of detecting potassium deficiency (by serum levels) cannot be unequivocally relied upon. However caused or manifested, potassium deficiency must be judiciously corrected. Replacement dosages are, thus far, on an empiric basis because of the inability to determine cellular levels. With adequate renal output, the dangers of overdosage are lessened if sufficiently diluted solutions are given. Induced hyperkalemia can be avoided by not exceeding a concentration of 6 grams per liter (80 milliequivalents per liter) nor an inflow of more than one and one-half grams per hour. When indicated, potassium replacement must be adequate and if adequate response is not obtained by conservative doses, the schedule must be increased. It was with trepidation that we gave 8 grams in one day but others have reported even larger doses as being beneficial under appropriate circumstances.

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ABSTRACTS ON NUTRITION

RUBBO, S. D.: *Vitamin B₁₂: a short summary.* Med. J. Australia, Mar. 7, 1953, 324-326.

Rubbo presents an unusually succinct summary of the present knowledge concerning vitamin B₁₂. Vitamins B_{12a}, B_{12b}, B_{12c} and B_{12d} are all active. The molecular weight of B₁₂ is about 1300, each molecule containing one atom of cobalt and one of phosphorus. B₁₂ is an essential growth factor for three micro-organisms—*Lactobacillus lactis* Dornier, *Lactobacillus leichmannii* and *Engleina gracilis* (alga). Bacteria and worms in the gut of the pernicious anemia subject may absorb B₁₂ far beyond their requirements, and tapeworms in the small bowel may produce a B₁₂ deficiency and associated anemia. B₁₂ is Castle's extrinsic factor, and on oral administration requires intrinsic factor to make it absorbable. "Apoerythrein," a non-dialyzable substance recovered from normal gastric juice combines with B₁₂, but it is not certain that it is identical with intrinsic factor. When B₁₂ is injected intramuscularly, 50 percent to 70 percent is excreted in the urine in 8 hours in a free state, after which it is bound and persists in circulation for a variable period prior to tissue storage. The bound form is not excreted in the urine. Folic acid, folinic acid and B₁₂ have been identified as being essential to hematopoiesis. An absence of any of these catalysts or their substrates will result in impaired blood formation. Thymine and thymidine are related to the processes by which amino acids are converted to nucleotides. Vitamin B₁₂ probably catalyzes the synthesis of thymidine.

GHOSE, C.: *Studies on metabolism of calcium, inorganic phosphorus and cholesterol in pregnancy with anemia.* J. Indian Med. Assn., XXII, 6, Mar. 1953, 228-233.

Serum calcium is reduced in severe cases of the macrocytic anemia of pregnancy, but serum organic phosphorus does not change in pregnancy anemias. Serum cholesterol is reduced in anemias of pregnancy (both free and ester fraction). The reduction bears a direct relationship to the fall in blood count.

LAHIRI, S. C.: *Gastric hydrochloric acid and blood chloride.* J. Indian Med. Assn., XXII, 6, March 1953, 235-240.

In many persons with low blood chloride levels, due to cholera or low salt diet, deficiency of the acid gastric secretion was found. In anemias, even though severe, the gastric acid level was normal, but in those in whom it was reduced there was an associated lowered blood chloride level although the converse was not always true. The majority of persons with hypersecretion had subnormal blood and urinary chlorides, due to excessive drainage of the latter through the gastric juice.

HOBSON, W. AND BLACKBURN, E. K.: *Hemoglobin levels in a group of elderly persons living at home alone or with spouse.* Brit. Med. J., Mar. 21, 1953, 647-649.

Hemoglobin values were determined in 177 men and

246 women, ages 61 to 87, who were living at home either alone or with spouse. There was a significant downward trend over a certain age range, the males having a mean level of 14.4 gms. per 100 ml., the females 13.8 gms. per 100 ml. Pulmonary emphysema did not produce high hemoglobin readings. About 6 percent had levels of 11.7 gms. per 100 ml. There were 21 cases of iron deficiency anemia and 4 cases of macrocytic anemia. Poor diet was the main contributing factor to the anemia, although rheumatoid arthritis also was a strong contender. Apathy and a low income were the chief reasons for the poor diet.

HAWKING, F.: *Milk diet, p-aminobenzoic acid, and malaria (P. Berghei).* B. M. J., May 30, 1953, 1201-1202.

It had previously been noted that rats on a milk diet do not properly develop infections of *Plasmodium berghei*. It was supposed that milk contained something which could inhibit the development of the asexual phase of blood-transmitted *P. berghei* in the rat. Hawking suspected, on the contrary, that milk might lack something essential to the growth of the malarial organism. This turned out to be para-aminobenzoic acid. By adding this substance to the milk diet, the organism developed in rats with the usual virulence. The conclusion was that PABA was essential to the growth of the malarial organism.

BROWN, D. AND HOLMAN, R. L.: *A trial of goat's milk in eczema in childhood.* B. M. J., May 30, 1953, 1202-1203.

An experiment was made with children having eczema to see if improvement could follow the substitution of goat's milk for cow's milk. No effect on the eczema was noted. None of these patients showed cutaneous hypersensitivity with scratch or patch tests with cow's or goat's milk.

FIGUEROA, W. G., SARGENT, F., IMPERIALE, L., MOREY, G. R., PAYNTER, C. R., VORHAUS, L. J. AND KARK, R. M.: *Lack of avitaminosis among alcoholics: its relation to fortification of cereal products and the general nutritional status of the population.* J. Clin. Nutrition, 1, 3, Mar. 1953, 179-199.

16,000 inmates of the House of Correction of the City of Chicago (The Bridewell), 56 of whom were alcoholics, were screened in 1948-9 for classical nutritional deficiency syndromes. 451 newly admitted alcoholics were given careful nutritional examinations during the "pellagra season," and detailed, serial, physiological and biochemical observations were made on 24 selected alcoholics before and after treatment. Hemoglobin average was high, but about a third of the alcoholics were grossly underweight. The fasting hour excretion of thiamin and riboflavin was normal. Only 2 cases with pellagra were found, only one with possible beriberi, three with florid ariboflavinosis, one with Wernicke's encephalopathy, and 7 with possible nutritional polyneuropathy. In all, only 2.2 percent of

the men were considered to have clinical evidence of avitaminosis.

To explain this unexpectedly low incidence of avitaminosis, one must fall back upon the fact that the vitamin enrichment of bread was begun in Chicago in 1940-41. Alcoholic pellagra practically disappeared from Cook County Hospital in 1942-43 when niacin,

for flour enrichment, was first made by the ton. The alcoholic eats mainly fortified bread, and the authors conclude that this food habit has been the most significant factor contributing to the present surprising lack of avitaminosis among alcoholics. On the basis of these observations, the position is taken that primary avitaminoses are uncommon in the United States.

EDITORIAL

DRUG ALLERGY

Every once in a while, almost every practitioner has occasion to be alarmed by the appearance of dangerous (and sometimes fatal) symptoms following the administration of drugs which, to the majority of patients, are certainly innocuous. Ethan Allan Brown (1) has recently taken time to collect from the literature many instances of hypersensitivity to drug therapy. His article cannot be briefly condensed and should be read by everyone. The list of antigenic drugs is surprising. Even aspirin occasionally kills a patient. Today, of course, the physician usually has become careful in his treatment, because of the large number of synthetic products which possess the power, in certain individuals, of causing extremely serious illness, and even death. We are becoming increasingly aware, for example, of the frightful reactions which sometimes occur to the antibiotics. Some of the delayed reactions to penicillin are terrific in their impact on the patient and once seen, give the physician pause, particularly when

large amounts of the substance are to be used. But it is not just the antibiotics which possess this occasional antigenic power. It is well known that the injection of thiamine intravenously may at times produce sudden collapse and death. While the intravenous injection of almost any substance is more likely to produce illness of an anaphylactic nature than subcutaneous or intramuscular injection, it must be remembered that oral administration also is quite capable of producing untoward or dangerous symptoms, usually when least suspected. As Brown remarks, a careful study of drug allergy has a tendency to render the physician a therapeutic nihilist. Today, as never before, there is an overwhelming vogue for injecting drugs, and at times this is unavoidable. At other times, when the oral route suffices, it should be employed. No matter what we prescribe, we should all be prepared for the occasional, unfortunate and highly regrettable reactions that may occur.

(1) Brown, E. A.: Drug allergy. *Quart. Rev. Allergy and Applied Immunology*, Vol. 7, March 1953, 51-82.

BOOK REVIEWS

DISEASES OF THE ESOPHAGUS (DIE KRANKHEITEN DER SPEISEROHRE), Hugo Starck. Verlag Dr. Dietrich Steinkopf, Darmstadt 1952. 145 pages, 69 illustrations.

Starck discusses the diseases of the esophagus from his vast personal experience. The book contains a general and a special part. The author refrains from adding a bibliography and refers to the handbooks and his former publications. The different diseases are discussed such as neuroses, erosive esophagitis, strictures and cardiospasm. The most extensive discussion is devoted to the dilatations of the esophagus. The book is written in German and, mostly, for the readers of the German medical literature, therefore, the newer American work and interest in varices, or Schindler's symptom of Krause's ulcer are either only superficially discussed or not mentioned at all. The book is written for the student and the general practitioner, but is also use-

ful for the gastroenterologist. It is very easy to understand. The reproductions of the roentgenograms, specimens, and the esophagoscopic aspects are very good and informative. We are recommending the book to all those interested in this field. We want to congratulate Starck on his book, for it summarizes his life long important work.

Franz J. Lust

GASTROENTEROLOGIA. Marcos Meeroff, M. D. Editorial Stileograf, Buenos Aires, 1953.

In about 60 pages Meeroff presents an unusually condensed and yet satisfactory work on gastroenterology, which is up-to-the-minute in every respect. The book is practical and devotes an unusual amount of space to treatment. No doubt it will eventually be translated into English.

GENERAL ABSTRACTS OF CURRENT LITERATURE

DRAGSTEDT, L. R.: *The physiology of gastric secretion and the peptic ulcer problem.* Proc. Staff Meet. Mayo Clin., 27, 26, Dec. 17, 1952, 546-552.

In animals it was found that an exaggerated secretion of gastric juice resulted when the antrum of the stomach was transplanted into the colon so as to form an artificial "diverticulum" of the colon. Such exaggerated secretion produced peptic ulceration in these experimental animals. When hypersecretion of gastric juice is produced, either by the exaggerated activity of the nervous phase of gastric secretion, or of the antral or hormonal phase, progressive peptic ulcers may be produced in the stomach or adjacent to a gastrointestinal anastomosis. What part does hyperfunction of the antrum play in human ulcer? Such action is possible but has not been demonstrated.

SMITH, L. A.: *Present day problems in appendicitis from the internist's viewpoint.* Proc. Staff Meet. Mayo Clin., Jan. 14, 1953, 28, 1, 1-5.

When a diagnosis of acute appendicitis can be made, operation should be done, although the availability of antibiotics seems to have softened some of the urgency formerly associated with the disease. The difficulties in diagnosis are so common that it might be said that *appendicitis is unusual when the symptoms are typical.* Usually mid-abdominal pain soon centers in the right lower quadrant, but, in cases of retroperitoneal appendicitis it locates in the right flank. Such complications as spreading peritonitis, pyelophlebitis, subphrenic abscess and residual pelvic abscesses are responsible for most of the deaths. Antibiotic therapy in which streptomycin is combined with penicillin or aureomycin or terramycin are used has tremendously reduced mortality in complicated cases, but sound surgical technique is needed in management of complications.

FELDMAN, M. AND MYERS, P.: *The diagnostic evaluation of erect positioning in cholecystography.* Radiology, 60, 2, Feb. 1953, 222-225.

In cases in which the history suggests gallstones but the usual prone cholecystograms fail to show any stones, the erect position should be used. Floating stones, or minute stones, are more likely to be found by this method.

DUNNE, E. F., JENSEN, E. H. AND HUGHES, C. R.: *Telepaque: a new medium for cholecystography.* Radiology, 60, 2, Feb. 1953, 210-214.

The use of Telepaque on 542 cases at the Cleveland Clinic is described. So far as visualization of the gallbladder was concerned, Telepaque gave more excellent results than Priodax, and produced noticeably less unpleasant side effects.

WHITEHOUSE, W. M. AND MARTIN, O.: *A comparative clinical study of Priodax and telepaque, including 1,000 examinations.* Radiology, 60, 2, Feb. 1953, 215-221.

The Department of Roentgenology, University of Michigan, found that Telepaque gave fewer side effects

than equal doses of Priodax. More excellent shadows also are obtained in over 65 percent of cases in which both media were used. Telepaque affords better demonstration of radiolucent stones but owing to the density of the shadow, an opaque stone may occasionally be obscured.

GORDON-TAYLOR, SIR G.: *The management of the complications of peptic ulcer.* Med. J. Australia, Jan. 17, 1953, 55-59.

Years ago, the surgeon was not called in, in cases of bleeding ulcer, until the patient was practically moribund. Even prominent physicians were frequently under the impression that ulcer hemorrhage never terminated fatally, although Gordon-Taylor himself espoused surgery (in suitable cases) from the beginning and has lived to see his ideas widely accepted. Any patient who is bleeding for the second time from a peptic ulcer, and who is over 50 years of age, requires surgery. In all cases, once bleeding begins, the first 48 hours are critical since 65 percent of deaths occur by the third day. In perforation, the excellent results of radical surgery (partial gastrectomy) undertaken soon after the perforation, causes Gordon-Taylor to wonder why anyone would elect to be treated by medical means alone. He warns against doing partial gastric resections on women (unless a cancer is present) because of the severe microcytic anemia that is likely to follow. It should be a "criminal offense to perform gastrectomy on a woman, except under special circumstances."

GHOSH, P. K.: *Abdominal tuberculosis.* Calcutta Med. J., 49, 9, Sept. 1952, 362-366.

Three varieties of abdominal tuberculosis are described—entero-colic, tabes mesenterica, and peritoneal T.B. Pneumoperitoneum followed by peritoneoscopy is valuable in the diagnosis. The intestinal type usually is due to swallowing infected sputum, and the terminal ileum is the commonest site. Tabes mesenterica is found in children, and the enlarged glands can be felt on the right side of the abdomen. In peritoneal T.B., the ascitic form is the more common. Streptomycin and PAS, plus vitamins, form the basis of treatment. The author doubts the value of calcium.

GOULSTON, S.: *The treatment of peptic ulcer.* Med. J. Australia, Feb. 28, 1953.

The use of surgery in the treatment of peptic ulcer is, as yet, not as common in Australia as in Britain and the U.S.A. In duodenal ulcer (uncomplicated) Goulston relies on rest, frequent feedings, alkalis, and atropine. The latter drug, if given in fairly large doses, does as much good as Bantline. Tobacco is interdicted. A careful physiological study of each individual is important. The intragastric drip at night is more disturbing than an alarm clock and some alkali beside the bed. Gastric ulcer is as common in women as men and Goulston feels that malnutrition is a factor in the etiology. Surgery is better here because of the danger of cancer. Goulston's treatment is preferably medical in all peptic

ulcers, but subtotal gastrectomy is done when necessary. He emphasizes the poorer prognosis in hemorrhage with advancing years. Circulatory failure should be treated promptly, as one of the sequelae is blindness. He feels that perforation is a surgical problem.

RAPPAPORT, E. M., ALPER, A. AND RAPPAPORT, E. O.: *Failure of surgery to relieve symptoms in prolapse of the gastric mucosa through the pylorus.* Ann. Int. Med., 38, 2, Feb. 1953, 224-233.

The authors present 4 cases who were treated surgically for symptoms presumed to be due to prolapsing gastric mucosa, but in whom the symptoms later returned,—whether a simple excision or a subtotal gastrectomy had been done. They believe that the symptoms are not related to the prolapse, but are "psychosomatic." However, in cases where hemorrhage is associated with mucous membrane prolapse, a subtotal gastric resection should be done in any case.

DEARING, W. H. AND HEILMAN, F. R.: *Micrococcic (staphylococcic) enteritis as a complication of antibiotic therapy.* Proc. Staff Meet. Mayo Clin., 28, 5, Mar. 11, 1953.

Resistant strains of micrococcus pyogenes (staphylococci) have developed in certain hospitalized patients as a result of the administration of aureomycin or terramycin. These resistant strains when present in the intestine in more or less pure culture, may produce varying degrees of gastrointestinal and systemic reaction, which may be severe in some cases. Administration of erythromycin in doses of 300 to 400 mg. four times daily by mouth has eliminated these resistant strains from the gastrointestinal tract and promptly alleviated the local and systemic reactions. (Suggestive, but not conclusive evidence was presented to show that this micrococcic enterotoxic reaction is not necessarily related to pseudo-membranous enterocolitis).

ROBERTS, J. M.: *Cholesterol and cystic duct obstruction in pathogenesis of gall stones.* Northwest Med., 52, 3, Mar. 1953, 208-212.

Obstruction, as well as disturbed cholesterol metabolism, must be present to explain many cases of gall-bladder disease and gallstones. Drainage may be hindered by tortuosity of the cystic duct, by the valves of Heister, by abnormal sympathetic stimulation, or by other causes. Fifteen percent of a series of 73 patients were found to have marked emotional disturbance. Associated coronary disease was found in 9.6 percent. The influence of inflammation is being relegated to a comparatively minor role.

BARTLETT, R. W.: *Massive upper gastro-intestinal hemorrhage—its diagnosis and management.* Mississippi Valley Med. J., 75, 2, March 1953, 72-75.

In most cases of severe bleeding from the upper gastro-intestinal tract, successful treatment will consist in massive whole blood transfusions given frequently enough to keep the blood pressure and blood counts reasonably high. (In 10 to 15 percent of bleeding ulcers, the hemorrhage fails to stop within 48 hours, so that immediate surgery is required). In addition to large and frequent blood transfusions, the Meulengracht diet is indicated, and also adequate sedation. The x-ray

study of the upper G. I. tract is today practiced even during acute bleeding, when localization is important. Bartlett describes esophageal tamponade in cases of acute bleeding from esophageal varices in cirrhosis of the liver.

JONES, F. AVERY: *The management of complications of peptic ulcer.* Med. J. Australia, Jan. 17, 1953, 49-55.

In every series of admissions for acute perforations, all three methods of management,—medical, simple closure, and partial gastrectomy—will have a proper place, if best results are to be obtained. Under the most strict and expert medical management, a 9 percent mortality may be expected. The author has recently done 30 immediate partial gastrectomies without a single death.

ROACH, F. J., SLOAN, R. D. AND MORGAN, R. H.: *Detection of gastric carcinoma by photofluorographic method.* Am. J. Roent. Rad. Ther. 67, 1, 68, Jan. 1952.

The authors report a definite failure of the photofluorographic method to be of practical value in reducing the death rate from gastric malignancy. In 29 months, they examined 10,000 patients at The Johns Hopkins Hospital, 40 years of age and over. The number of individuals with early neoplastic disease is relatively small, being one per 476 examinations, or 0.2% in their series. Furthermore, it has been experienced that only a few of these can be persuaded to submit themselves to surgery prior to the development of symptoms. In this series, 1,209 cases, or 13.3%, had standard gastrointestinal series in addition to the miniature studies. In this group there were only 17 cases in whom the miniature studies were interpreted as showing a normal stomach, only to have the standard examination reveal the presence of gastric pathology. The false positives were 25.4%. The true incidence of gastric pathology in this series is difficult to evaluate. If one takes only those cases in whom lesions detected by the miniature studies were actually confirmed by standard examinations the over-all incidence is 1.3%, or 1 in 79 examinations. In 47.8% the duodenal bulb was inadequately visualized for diagnostic purposes. It shows that one thorough examination is better than many mass examinations.

Franz J. Lust.

WAPSHAW, H.: *The pancreatic side-effects of morphine.* Brit. Med. J., Feb. 14, 1953, 373-375.

In 84 human subjects, following the administration of morphine, the serum-enzyme concentrations (amylase and lipase) of the blood were significantly raised in 39 percent. These changes were probably due to a state of secretion-retention within the pancreas, caused by contraction of the sphincter of Oddi and consequent absorption of the enzymes into the blood.

SMITHER, W. J.: *Gastro-enteritis in general practice.* Brit. Med. J., Feb. 14, 1953, 376-378.

The author investigated 90 unselected cases of acute gastro-enteritis occurring over a period of 9 months in an urban practice. In by far the greatest number of these no pathogenic organisms were found. The com-

monest specific organism isolated was *Sh. sonnei*. *Pr. vulgaris* was the next most common. Only one case of infection with *Salm. typhi-murium* was found. Arguments are advanced for the belief that staphylococcal food poisoning is the most common cause of mild gastro-enteritis.

BURKE, J.: *The treatment of steatorrhea in Crohn's disease*. Brit. Med. J., Jan. 31, 1953, 239-242.

The author describes 3 cases which were probably correctly diagnosed as regional ileitis. In all three, steatorrhea, malnutrition and anemia were present. A high protein diet led to great improvement, indicated by a gain in weight and restoration to normal activity. The value of intravenous iron for the correction of hypochromic anemia was demonstrated. Since steatorrhea is often overlooked in this disease, fecal fat estimations are recommended. In Britain, persons with proved steatorrhea are eligible for extra meat rations.

DEDICK, A. P. AND COLLINS, L. C.: *The roentgen diagnosis of bleeding lesions of the small intestine*. Am. J. Roentgen., Rad. Ther. and Nuclear Med., 69, 6, June 1953, 926-935.

In gastrointestinal bleeding, on failing to find the cause in the stomach, duodenum or colon, the small bowel should be carefully examined. The paucity of physical findings should not prevent such examination if the patient has bleeding or unexplained anemia. The authors demonstrate that relatively small lesions in the jejunum and ileum can be recognized by careful radiological technique. Routine examination of the small intestine following a barium meal is the method of choice, but when this fails to reveal a lesion, the judicious use of intestinal intubation with injection of barium through the tube will demonstrate lesions in an additional number of patients. Pressure technique is described.

ROSZA, S. AND GROSS, R. L.: *Intrauterine perforation of Meckel's diverticulum*. Am. J. Roentgen., Rad. Ther. and Nuclear Med., 69, 6, June 1953, 944-947.

The only case in medical history of intrauterine perforation of a Meckel's diverticulum is presented. The x-ray findings resemble those of meconium ileus. The child died 9 hours after delivery.

DICK, E. T.: *Long term survival following partial gastrectomy for carcinoma of the stomach*. New Zealand M. J., 11, 286, Dec. 1952, p. 417.

Dick reports the case of a man in good health, (except for emphysema) 27 years following a partial gastrectomy for a pyloric lesion which was shown histologically to be an adenocarcinoma. At the time of the operation the enlarged lymph nodes in the neighborhood of the lesion were removed but did not show any histological evidence of malignancy.

FENWICK, T.: *Familial hypertrophic pyloric stenosis*. Brit. Med. J., July 4, 1953, 12-14.

Fenwick reports 4 cases of hypertrophic pyloric stenosis in one family. The incidence was confined to male members of two generations—one in adult life and three in infancy. Fenwick contends that the adult and infantile disease are one and the same. Surgical treatment in the adult should be a Billroth I gastrectomy or pylorectomy.

BISHOP, JAMES F.: *Irritable colon: symptom or clinical entity?* Miss. Valley Med. J., 75, 4, July 1953, 105-107.

Bishop emphasizes the fact that the nervous colon is merely an expression of nervousness or some emotion. He is somewhat iconoclastic with respect to dieting, and advises a "normal" diet. Sedatives are of great importance. Reassurance and an understanding of the patient himself is invaluable.

PALMER, E. D. AND BUCHANAN, D. P.: *On the ischemic basis of peptic ulcer. I. Historical definition of present status*. Ann. Int. Med., 38, 6, June 1953, 1187-1205.

In a rather "difficult" paper, the authors make an argument that peptic ulcer must have its origin in an erosion or necrotic area, and that the production of such an area probably depends on the nature of the arteriovenous anastomoses within the gastric wall. This arteriovenous shunt system operates under control of the autonomic nervous system and is called into play under certain conditions of stress. They admit that the acid-pepsin element keeps an ulcer "going" but that it does not initiate it. To produce focal ulcerogenic ischemia, the native arteriovenous shunt mechanism is the only one thus far demonstrated to be capable of it. Investigation is under way to elucidate this possible etiological factor and to bring it under control.

AYE, R. C.: *Peptic ulcers in children*. Radiology, 61, 1, July 1953, 32-38.

Four cases of chronic peptic ulcer are reported occurring between the ages of 3 and 1, one gastric and three duodenal. In all these cases an emotional factor was present. The incidence of duodenal ulcers exceeds that of gastric ulcers, with ratios given as 3 to 1 and 7 to 1. Chronic gastric ulcer in childhood is especially rare.

HUNTER, H. L. AND RAPP, R.: *Symptomatic hepato-diaphragmatic interposition of the colon*. Radiology, 61, 1, July 1953, 67-70.

The authors contend that interposition of the colon between the liver and diaphragm can occasionally be tentatively diagnosed by history and physical examination. Non-fixed interposition is occasionally reduced by barium enema, as demonstrated in a case presented, and at least one other case in the literature.

MEBARAL CALLED MOST EFFECTIVE SEDATIVE FOR DELIRIUM TREMENS

The tension and panicky fears experienced by alcoholics in a state of delirium tremens can be most effectively calmed with Mebaral, a long-acting sedative, according to Dr. Jackson A. Smith, professor of psychiatry, Baylor University College of Medicine, Houston, Texas. A recognized authority on alcoholism, Dr. Smith is director of the Alcoholic Clinic at Jefferson Davis Hospital.

Mebaral is a sedative of choice in controlling an alcoholic's "restlessness, apprehension and sleeplessness" during delirium tremens, the toxic state which has an average reported mortality rate of about five per cent. The mortality in delirium tremens complicated by head injuries, infection or systemic disease has been reported as high as 37 per cent, Dr. Smith states.

His observations are published in a monograph in the July 1953 issue of *American Practitioner*, titled: "Alcoholism, Causes and Methods of Treatment."

Discussing methods of treatment during the "delirious and hallucinatory stage," Dr. Smith emphasized that choice of sedatives presented a medical problem.

"The short-acting barbiturates are contraindicated due to the danger of habituation in the alcoholic, and because they may increase the confusion in inadequate dosage. Those barbiturates which are destroyed in the liver are not indicated if the liver disease is marked."

He says that Mebaral, known chemically as N-methylethylphenyl barbituric acid, is the sedative of choice since it "has not been found to be habituating, it produces no euphoria and is a good supplement to other, more drastic hypnotics." A dosage of three grains is recommended during the first 48 hours of treatment, and can be reduced to one and one-half grains after meals and on retiring.

Dr. Smith adds that Mebaral "is a good anticonvulsant and is indicated in those patients with a history of seizures occurring when they are delirious." The drug is supplied by Winthrop-Stearns Inc.

First consideration in treatment should be given to correction of evident physical abnormalities. If possible, restraint should be avoided, but is indicated if there is dan-

ger that the patient may harm himself. Systemic dehydration and malnutrition should be handled by intravenous feeding of a glucose-vitamin solution, if the patient is unable to take and retain food by mouth, Dr. Smith states.

In a section devoted to psychotherapeutic measures, he emphasizes the need to "go beyond the fact that the patient drinks pathologically into the motives that cause him to drink."

NEW DRUG REPORTED EFFECTIVE IN STUBBORN PROTEUS INFECTIONS

A new chemotherapeutic agent, Furadantin, was described as a valuable addition to the drugs available for treatment of urinary tract infections and as "particularly useful in the stubborn Proteus infections" by Dr. Grayson Carroll, associate professor of clinical urology, St. Louis University Medical School, in a report to the American Urological Association, St. Louis (on May 12, 1953).

Clinical studies of 79 patients on Furadantin therapy showed cultures of the urine to be negative in 53 cases. Proteus was the infecting organism in 10 cases, of which 9 were controlled. "The only untoward symptoms noted in patients administered the drug were nausea and, to a lesser degree, vomiting," Dr. Carroll reported. "Dizziness, headache, diarrhea, itching, paraesthesia, often seen as side reactions with other drugs, have not been observed in patients taking Furadantin." The drug is the first of the nitrofurans designed for systemic use.

DO COCCIDIA DEVELOP RESISTANCE TO DRUGS?

It is generally recognized that many people, after continued dosage, develop a resistance to antibiotics. Dr. Paul D. Harwood of Ashland, Ohio, initiated a study to determine whether or not chickens treated with drugs for the prevention and control of cecal coccidiosis developed resistance to the drug as a result of its continued use.

Dr. Harwood, head of research at Dr. Hess & Clark, conducted research with hundreds of chicks using two different drugs, nitrofurazone and sulfamerazine. Both of these drugs are now being used effectively in medicated feeds by poultry raisers

for coccidiosis prevention and control.

Coccidia of four different strains were used by Dr. Harwood, and all four strains were still fully susceptible to both drugs. If there were resistance to the drugs, this would be indicated by higher chick mortality among treated birds inoculated with newly isolated cultures of coccidia that had been exposed to prolonged drug treatment.

"Therefore, no drug-fastness was detected by the methods employed," Dr. Harwood states. "Under the conditions of these experiments, the prophylactic levels of nitrofurazone proved much more effective for preventing deaths from experimental coccidiosis than the prophylactic levels of sulfamerazine."*

*Dr. Harwood's paper appears in "The Journal of Parasitology," June 1953.

GREEK GOVERNMENT EXTENDS OFFICIAL THANKS TO PARKE-DAVIS FOR GIFT OF CHLOROMYCETIN

Detroit.—The Greek Government has officially extended appreciation to Parke, Davis & Company for the firm's donation of Chloromycetin to the earthquake-stricken Ionian Islands.

W. R. Jeeves, vice president and director of overseas operations, said today the Company's London office had received a letter from J. A. Phrantzes, Charge d'Affaires, Greek embassy, London, which said in part:

"I have received instructions from my Government to express to you their deep appreciation and warmest thanks for the most generous and valuable gift of Chloromycetin which your Company has so kindly despatched to Greece for the relief of the earthquake victims."

"I also wish to add my personal thanks for the immediate and effective way in which your Company has contributed to the relief of the unfortunate inhabitants of the Ionian Islands."

The series of earthquakes last month severely damaged the islands, leaving hundreds dead and several thousand homeless.

ANIMAL EXPERIMENTATION

The world's only national anti-vivisection law, adopted early in

the Hitler regime, is still in effect in Germany.

Discovery of the unique statute was made through an international survey of animal experimentation laws conducted by the National Society for Medical Research, Chicago, which describes the law in its Bulletin, published recently.

The Society notes that the law's effect was to ban all use of animals in medical school teaching and in the training of surgeons. Also, it placed German scientific research under stringent political control.

Since the law's enactment in 1933 over Hitler's signature, Germany has dropped from a leading position almost to the bottom of the world list in biological research, the article states.

INFANTILE PARALYSIS

Dr. Henry W. Kumm of Chocorna, N. H., and New York City, has been appointed director of research of the National Foundation for Infantile Paralysis, it was announced today by Basil O'Connor, president.

Dr. Kumm, who had spent 23 years on the staff of the Rockefeller Foundation for Medical Research before joining the National Foundation in July, 1951, replaces Dr. Harry M. Weaver of Bedford Village, N. Y., who has resigned.

Well known for his part in the Rockefeller Foundation investigations leading to the control of yellow fever, Dr. Kumm also has done extensive work in the study of modes of transmission of yaws and the control of malaria. He conducted field studies of the epidemiology of yellow fever in Nigeria, W. Africa, and was director of the Yellow Fever Laboratory in Rio de Janeiro from March, 1945 until that organization was turned over to the government of Brazil at the end of 1945. He spent two years in the British West Indies with the Jamaica Yaws Commission and represented the Rockefeller Foundation in malaria and yellow fever control work in Costa Rica, El Salvador, Panama, Colombia and Brazil.

During World War II he served as civilian consultant to the Surgeon General of the U. S. Army in Italy, directing field studies of the use of DDT against malarial mosquitoes

in the marshes near Rome and Naples.

Dr. Kumm was born in Wiesbaden, Germany, son of the eminent African explorer and geographer, Dr. H. Karl W. Kumm. He came to this country from England and became an American citizen in 1945. He received his B.S. from Haverford College in Pennsylvania, his M.D. and Doctor of Public Health from Johns Hopkins University. He also won a diploma in Tropical Medicine from the Conjoint Board of England.

He is a member of the American Medical Association, the Medical Societies of the County of New York and the State of New York, the American Association for the Advancement of Science, the American Society of Tropical Medicine and Hygiene and the Royal Society of Tropical Medicine and Hygiene of England.

He is the author of some 50 papers on tropical medicine and poliomyelitis.

Dr. Kumm is married to the former Miss Joyce Beale of London, England, and is the father of two sons and a daughter: William Howard Kumm, electronics engineer with the Westinghouse Corporation in Baltimore, Md.; Frederick Kumm, a freshman at Dartmouth College, Hanover, N. H.; and Miss Jocelyn Anne Kumm, a senior at Smith College, Northampton, Mass. Dr. and Mrs. Kumm are members of the Manhattan Post, Ground Observers' Corps of the U. S. Air Force.

DISEASE-FREE "ISLANDS" ARE ONE OF GREATEST MYSTERIES IN MODERN SCIENCE, TROPICAL DISEASES AUTHORITY SAYS

Schenectady, N. Y.—Disease-free "islands" are one of the greatest mysteries unsolved by modern science, according to Dr. Eugene H. Payne of Parke, Davis & Company, a leading authority on tropical diseases.

Speaking on the General Electric Science Forum over radio station WGY, he pointed out that even though it is surrounded by malaria-infested areas, one Brazil town of 15,000 people has been absolutely free of this disease for at least a century.

Dr. Payne related that a number of the land-islands free of disease have been found in South America. Some of these areas are void of heart disease and hookworm though adjacent sectors report many such cases. Similarly, he said, insanity is practically unknown to Bolivians.

He said that many theories have been developed as to why this immunity exists but none has as yet been proven.

Dr. Payne, a member of the Parke-Davis Department of Clinical Investigation stressed the importance of studying these remote peoples while they remain static. Once they mingle with other groups, science will lose its chance to determine how they remain free from diseases which infest regions around them.

HONDURAS PHYSICIAN REPORTS ON SUCCESSFUL CAMOQUIN USE TO INTERNATIONAL MALARIA CONGRESS AT ISTANBUL, TURKEY

Istanbul, Turkey. — Camoquin was used successfully to treat 500 patients with malaria, a Honduras physician reported.

Dr. Mark T. Hoekenga of La Lima, Honduras, Hospital told the International Congress of Malaria and Tropical Medicine convening here:

"... it is apparent that amodiaquin (Camoquin) is the drug of choice."

Dr. Hoekenga said 920 malaria patients were treated in this survey, including 500 who were given Camoquin. Three hundred and twenty patients received chloroquine, and 100 were treated with plaquein.

The physician told the Congress that amodiaquin (Camoquin) is "low in toxicity and has been used in many parts of the world with good results in dosages even smaller than those recommended for chloroquine."

He said, "Amodiaquin (Camoquin) was given to 500 patients divided into four groups according to single dosage used. The groups received: 0.4 Gm., 0.6 Gm., 0.8 Gm. or 1.0 Gm. respectively, of the base."

Oral temperature on all patients was recorded every four hours and, throughout hospitalization, thick

blood films were examined twice daily.

Of the 500 patients treated with Camoquin, there were only three who did not respond, all of whom had been treated by the 0.4 Gm. dosage. However, the physician pointed out these three responded promptly to a higher dose of the drug.

"In nearly all patients headache, malaise, vomiting, joint pains and other symptoms caused by malaria disappeared within 36 to 48 hours," the physician reported.

WYETH INTRODUCES PHENERGAN EXPECTORANT TROCHES WITHOUT CODEINE

Philadelphia, Sept. 10.—Because many physicians have expressed the need for a Phenergan Expectorant troche not containing codeine, for administration to children, troches without the narcotic are now available, it was announced today by Wyeth Laboratories.

As in the troche containing codeine, the new dose form provides local anesthetic action plus loosening of mucus for treatment of coughs and other minor irritations of the upper respiratory tract.

NEW PRESCRIPTION SPECIALTY:

THE PRODUCT IS: Phenergan Expectorant Troches (Plain) are pleasantly flavored troches containing promethazine and expectorant agents.

USE OF PRODUCT: For coughs associated with the common cold, minor infections of the upper respiratory tract, and minor throat irritations.

HOW ADMINISTERED: Orally. A troche is allowed to dissolve slowly in the mouth every four to six hours.

HOW SUPPLIED: Jars of 36.

MANUFACTURER: Wyeth, Philadelphia.

IMPROVED INJECTION TECHNIQUE NOT REQUIRING STERILIZATION INTRODUCED BY WYETH LABORATORIES

A new method of administering injectable drugs, eliminating the need for sterilized equipment and at the same time avoiding any pos-

sibility of contaminating the injection needle, will be introduced to the medical and allied professions, it was announced by Wyeth Laboratories.

The new dose unit is an improved Wyeth "Tubex," to which an injection needle is affixed, ready to use. A sterile rubber sleeve protecting the needle need not be removed until the moment of injection.

To use the new injection equipment, the physician loads the Tubex-needle unit into a syringe just like loading a shotgun. A twist of the wrist engages threads at both ends of the tube to provide two-way control. Then the sterile sleeve is removed just before the injection is made.

The syringe body need not be sterilized, since neither needle nor medicament can touch it.

The new Tubex is an improvement over injection methods now in general use. In one technique, the physician sterilizes a glass syringe and needle, then extracts the correct amount of medicament from a rubber-capped vial.

A more recent method, forerunner of the new Tubex, provides a measured dose of medicament with a needle packed separately in a sterile envelope. The physician must unwrap the needle and assemble it to the syringe, risking contamination of the needle in the process.

Both methods require that the syringe body be sterilized. Because it eliminates this requirement, the new Tubex is expected to gain quick popularity among busy doctors, dentists, and veterinarians. It will be especially valuable on house calls, where sterilizing facilities are not usually available.

The new Tubex units are to be used in a new version of the Tubex breech-loading syringes which Wyeth will provide at no charge with initial shipments to professional users. First products to be released in the new units are Biocillin "600"; Wycillin "300" and "600." Most of Wyeth's other injectable drugs will be available in the new Tubex units as soon as current stocks of old type are exhausted, a Wyeth spokesman said.

POLIO

The National Foundation for Infantile Paralysis announces the availability of a limited number of addi-

tional postdoctoral fellowships to candidates whose interests are research and teaching in medicine and the related biological and physical sciences. The purpose of these National Foundation fellowships is to increase the number of professional workers qualified to give leadership in the solution of basic and clinical research problems including those of poliomyelitis and other crippling diseases.

The fellowships cover a period of from one to five years. Stipends to Fellows range from \$3,600-\$7,000 a year, with marital and dependency status considered in determining individual awards. Institutions which accept Fellows receive additional compensation for expenses incurred in relation to their training programs.

Eligibility requirements include United States citizenship (or the declared intention of becoming a citizen), sound health and an M.D., Ph.D., or an equivalent degree.

Selection of candidates is made by a Fellowship Committee composed of leaders in the fields of medical research and professional education. The designation "Fellow of The National Foundation for Infantile Paralysis" will be given to successful candidates.

A total of 181 fellowship awards in these categories has been made by the National Foundation up to August 1, 1953.

Complete information concerning qualifications and applications may be obtained from Division of Professional Education, The National Foundation for Infantile Paralysis, 120 Broadway, New York 5, New York.

DETROIT MAN LED DELEGATION OF 30 AMERICANS TO INTERNATIONAL PHARMACEUTICAL MEETING IN PARIS

Detroit—John A. MacCartney of Detroit headed a delegation of 30 persons who represented the American Pharmaceutical Association at the 15th annual assembly of Federation Internationale Pharmaceutique in Paris Sept. 13-20.

MacCartney, first vice-president of the A.Ph.A. and trade relations manager for Parke, Davis & Company, left New York by plane Sept.

When diet restriction limits nutrition

Vitamins alone
are not always enough

Based on the well recognized concept of interrelationship in nutrition, "Clusivol" Capsules offer an extensive formulation of vitamins, minerals, and trace elements . . . factors likely to be lacking when restrictive diets are prescribed.

REDUCING DIETS
DIABETIC DIETS
GERIATRIC DIETS
POSTOPERATIVE DIETS
PEPTIC ULCER DIETS
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RHEUMATIC FEVER DIETS

2 "Clusivol" Capsules
(average daily dosage) provide:

Vitamin A (synthetic)	25,000 U.S.P. Units
Vitamin D (irradiated ergosterol)	2,000 U.S.P. Units
Vitamin C (ascorbic acid)	150.0 mg.
Thiamine HCl (B ₁)	10.0 mg.
Riboflavin (B ₂)	5.0 mg.
Pyridoxine HCl (B ₆)	1.0 mg.
Panthenol, equivalent to of calcium pantothenate	10.0 mg.
Vitamin B ₁₂ U.S.P. (crystalline)	2.0 mcg.
Folic acid	2.0 mg.
Nicotinamide	100.0 mg.
Vitamin E (as mixed tocopherols natural)	10.0 mg.
Inositol	30.0 mg.
Choline—from choline bitartrate	30.0 mg.
Biotin	0.1 mg.
d-Methionine	20.0 mg.
Cobalt—from cobalt sulfate	0.1 mg.
Copper—from copper sulfate	1.0 mg.
Fluorine—from calcium fluoride	0.025 mg.
Iron—from 4 gr. ferrous sulfate exsicc.	76.2 mg.
Calcium—from dicalcium phosphate	165.0 mg.
Manganese—from manganese sulfate	1.0 mg.
Iodine—from potassium iodide	0.15 mg.
Molybdenum—from sodium molybdate	0.2 mg.
Potassium—from potassium sulfate	5.0 mg.
Zinc—from zinc sulfate	1.2 mg.
Magnesium—from magnesium sulfate	6.0 mg.
Phosphorus—from dicalcium phosphate	127.4 mg.

"CLUSIVOL"® CAPSULES

No. 293—Supplied in bottles of 100 and 1,000.

Ayerst, McKenna & Harrison Limited
New York, N. Y. • Montreal, Canada



WYETH PRODUCTS IN CLINICAL APPLICATION

WYCHOL® in the correction of abnormal patterns of fat metabolism.

Clinicians frequently observe noteworthy subjective improvement in patients receiving lipotropic medication for various conditions.^{1,2} Empiric findings of this nature are abundantly supplemented by clinical and experimental observations indicating that: *Lipotropic substances can and do influence favorably certain abnormal patterns of lipid turnover.*

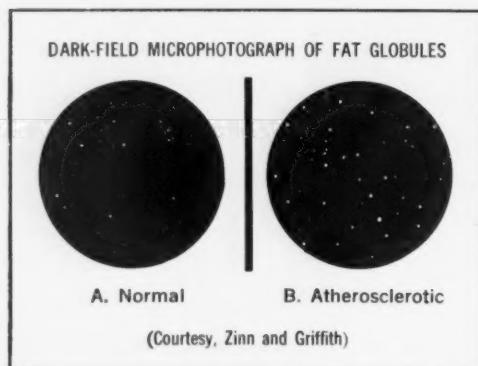
Confirmation of the value of lipotropic therapy in fatty infiltration of the liver is afforded by numerous published reports. These are perhaps best summarized by Polak's observation that

"The reversal of hepatic steatosis and the improvement of the patients' well-being justify fully the usage of lipotropics . . ."⁵

Effect in Atherosclerosis

A number of clinicians have reported that lipotropic factors aid in the reduction of hypercholesterolemia,⁶ and that their daily use favorably influences the mortality rate in coronary atherosclerosis.⁷

During the past few years, a great deal of experimental and clinical investigation has been directed to studies on etiologic factors in atherosclerosis. An important contributory factor is a high relative concentration of



(Courtesy, Zinn and Griffith)

chylomicrons—fat particles 0.3 micron in diameter or larger—in the circulating blood of the fasting patient.^{8,9} Recently, Labecki¹⁰ has shown that a nutritional lipotropic regimen continued over a period of several months influenced the ratio of these lipids profoundly "in the direction of apparent normality."

Lipotropic therapy lowers the chylomicron level.¹⁰

A potent lipotropic combination—Syrup WYCHOL, choline and inositol, Wyeth—provides in each tablespoonful (15 cc.), 3 Gm. choline base (equivalent to 7.5 Gm. choline dihydrogen citrate) *plus* 0.45 Gm. inositol. WYCHOL is pleasantly flavored to encourage patient acceptance. Dosage with WYCHOL may be conveniently adjusted to suit the individual case.

WYCHOL is supplied in bottles of 1 pint and is also available as Capsules WYCHOL in bottles of 100 and 1000.

A new Syrup WYCHOL B is now available for your use. It contains WYCHOL to which has been added vitamin B₁, 2.5 mg.; vitamin B₂, 0.5 mg.; vitamin B₆, 2.5 mg., and niacinamide, 10 mg., in each 3 teaspoonsfuls (15 cc.).

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PHILADELPHIA 2, PA.

11. Following the assembly, he visited the Parke-Davis laboratories at Hounslow, England, and returned to New York Sept. 22.

More than 1,000 pharmacists from 40 nations attended the assembly sessions in Palais de Chaillot. All phases of professional pharmacy were discussed. Besides talks of general interest by outstanding authorities, there were sessions for specialists, including directors of control laboratories, pharmaceutical editors, hospital pharmacists, pharmaceutical historians, military pharmacists and teachers.

MacCartney said Parke, Davis & Company would have an assembly exhibit featuring full-color art prints of oil paintings in the unique "History of Pharmacy" series. Commissioned by Parke-Davis as a tribute to the traditions of pharmacy, the paintings depict dramatic highlights from "Before The Dawn Of History" until about 1825. Others will be completed at a rate of six a year, and the unusual project is slated for completion in 1956.

A trip to Versailles will end the assembly program, MacCartney said.

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OCTOBER, 1953

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for peptic ulcer
or gastrointestinal
spasm

'TRICOLOID'
TRICYCLAMOL

A recently developed anticholinergic agent which has a marked effect on reducing gastrointestinal motility and spasm.

'TRICOLOID' affords relief, in most instances, within a few hours, from the gnawing pain associated with peptic ulcer.

'TRICOLOID' is recommended for the medical management of peptic ulcer and gastrointestinal spasm, as an adjunct to appropriate diet and antacids, as well as to therapy aimed at reduction of tension.

'Tricloid' 500 mg.
Compressed, sugar-coated

Bottles of 100

Please to take



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PARLUGUANTM FOR PEPTIC ULCER MANAGEMENT

and control of gastric hyperacidity

Now [Troches] Provide Effect of Intragastric Milk-Alkali [Drip]

Present day medical regimen is based on the generally accepted theory that to heal an uncomplicated gastroduodenal ulcer, hydrochloric acid should be neutralized. To reduce the acidity favors healing, as it most certainly favors relief of pain associated with ulcer symptoms.

The most effective method known for neutralizing stomach contents over long periods has been the continuous intragastric milk and alkali drip.

This method has practical disadvantages.

But now the principle and effect of the intragastric milk-alkali drip is provided by continuous sucking of PARLUGUAN buccal troches containing milk solids and non-systemic alkali.

PARLUGUAN buccal troches

- provide continuous acid neutralization
- promote healing of uncomplicated peptic ulcers
- reduce symptomatic ulcer pain
- strikingly reduce gastric acidity
- control pH levels for extended periods
- provide only 11 calories per troche
- are pleasant tasting

Also indicated for relief of gastric hyperacidity and gastritis.

DOSAGE: One-half hour after food is taken a PARLUGUAN troche should be placed in the mouth between the cheek and the gums and allowed to dissolve slowly over a period of 20 to 30 minutes. Up to 2 or 3 troches per hour may be required during the stage of ulcer activity. Follow-up treatment requires 1 to 2 troches between meals.

As an antacid for the temporary relief of gastric hyperacidity, 1 troche; repeat if necessary.



PARLUGUAN CONTAINS:

- Whole milk solids, fortified with dextrans and maltose
- Magnesium trisilicate
- Magnesium oxide
- Calcium carbonate
- Magnesium carbonate

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Patient enjoys beneficial
effect of intragastric milk-
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comfort of intubation.



Available in handy vials of 25 troches at all pharmacies.
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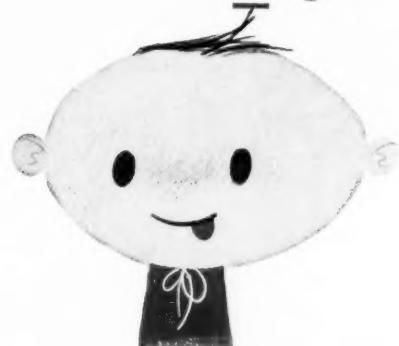
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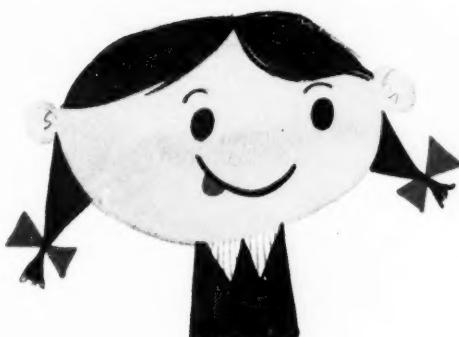
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that's what physicians and patients alike call these two favorite dosage forms of Terramycin because of their unsurpassed good taste. They're nonalcoholic — a treat for patients of all ages, with their pleasant raspberry taste. And they're often the dosage forms of first choice for infants, children and adults of all ages.

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Pediatric Drops

Each cc. contains 100 mg. of pure crystalline Terramycin. Supplied in 10 cc. bottles with special dropper calibrated at 25 mg. and 50 mg. May be administered directly or mixed with nonacidulated foods and liquids. Economical 1.0 gram size often provides the *total dose* required for treatment of infections of average severity in infants.

Supplied: Bottles of 1.0 Gm.

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Each 5 cc. teaspoonful contains 250 mg. of pure crystalline Terramycin. Effective against gram-positive and gram-negative bacteria, including the important *coli-aerogenes* group, *rickettsiae*, certain large viruses and protozoa.

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Childhood constipation deserves treatment which gently restores normal peristaltic movements; drastic elimination cannot permanently correct the condition and may be harmful to the child.

ROLE OF METAMUCIL® IN ESTABLISHING PROPER BOWEL HABITS IN CHILDREN

Metamucil's bland, demulcent bulk is a physiologic way to manage bowel dysfunction in youngsters.

Metamucil does more than merely clear the constipated bowel. When taken with adequate amounts of water, Metamucil's hydrophilic colloid has a proved corrective effect on the child's malfunctioning intestines. Use of Metamucil early in life assures a natural method of elimination and helps guard against formation of the "laxative habit" in later years.

Mixed with fruit juice, milk or the

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Metamucil is the highly refined mucilloid of *Plantago ovata* (50%), a seed of the psyllium group, combined with dextrose (50%) as a dispersing agent. It is accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

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